Metabolic and psychiatric genetics of anorexia nervosa

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Metabolic and psychiatric genetics of anorexia nervosa

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Abstract

Anorexia nervosa is a complex human trait that is primarily expressed in females but also observed in males. The disorder originates from an interplay of environmental factors with a genetic liability and develops most commonly around the time of puberty. Individuals with anorexia nervosa exhibit disordered eating behaviour as they severely restrict their calorie intake relative to their energy expenditure, and may engage in binge-eating and/or purging behaviour. Some individuals with anorexia nervosa exercise excessively to control their weight. These behaviours often coupled with distorted body perception and undue influence of body weight or shape on self-evaluation, result in extremely low and sometimes life-threatening body weight. No first line pharmacological treatment for anorexia nervosa is available, but psychotherapy coupled with therapeutic renourishment can be successful. Only 30-40% of individuals with anorexia nervosa seek treatment, and up to 30% of individuals develop a chronic or relapsing course. The mortality ratio of anorexia nervosa with up to 5.9 is one of the highest of all psychiatric disorders, therefore, new treatment options and preventive strategies are critically needed.

During an acute episode of anorexia nervosa, individuals evidence ~50% lower body fat, lower fat-free mass, including losses of bone mineral mass and alterations in biochemical markers. Phenotypically, these body composition alterations are associated with higher insulin sensitivity and cortisol concentrations, but with lower leptin, thyroid hormone, and estradiol concentrations. Most of these alterations tend to return to levels or concentrations seen in healthy controls, but sample sizes are small and follow up periods are short which underscores the need for deep biochemical phenotyping of anorexia nervosa patients through “omics” approaches.

As twin studies report heritabilities of anorexia nervosa between 32 and 74%, the next logical step was to perform genome-wide association studies to detect genomic loci that are associated with anorexia nervosa. Using the genome-wide approach, we explain 17% of the variance of anorexia nervosa (i.e., heritability) via the contribution of common genetic variants. We identify eight genomic loci associated with anorexia nervosa, and enrichment analysis presents evidence for an involvement of brain tissue in the illness. Analysis using genetic

correlations that are measures of genetic overlap between traits show that anorexia nervosa shares genomic variants with other psychiatric disorders corresponding to its comorbidity profile. Furthermore, anorexia nervosa shares genetics with metabolic traits, including high-density lipoprotein and insulin sensitivity. This sharing of underlying genetics motivates our reconceptualisation of anorexia nervosa as a metabo-psychiatric disorder, which generates a myriad hypotheses for future research endeavours.

Testing the significant genetic correlations of anorexia nervosa with psychiatric and metabolic traits for sex-dependence reveals that body fat percentage in females is more strongly genetically correlated with anorexia nervosa than in males. This suggests that a sex-dependent set of genetic variants is associated with anorexia nervosa and may partially contribute to the observed sex bias.

Other psychiatric traits do not show sex-dependent genetic correlations with body composition traits and do not genetically correlate with metabolic traits like cholesterol or insulin sensitivity. Additionally, anorexia nervosa and obsessive-compulsive disorder—highly genetically correlated with each other—are the only psychiatric disorders that share genetic variants with accelerometer measured physical activity. This combination of metabolic and energy homeostasis-related genetic correlations may be unique characteristics of anorexia nervosa and differentiate it from other psychiatric traits.

This new understanding of anorexia nervosa as a metabo-psychiatric disorder opens up new avenues for future research strategies and underscores the need to collect large international samples with deep phenotyping of not only psychological traits, but also metabolomic, proteomic, and lipidomic markers in anorexia nervosa patients. We strengthen the perspective that anorexia nervosa has a biological component which reduces the stigma associated with anorexia nervosa and set an example for future research on other eating disorders.

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Data used in the thesis from the UK Biobank were collected and partially quality controlled prior to the research described here. I was responsible for preparing the phenotypic and genetic data for the analyses and was responsible for all analyses conducted if not otherwise stated. To the best of my knowledge, the work presented here is original and my own work, except where acknowledged in the text.

Hunna Watson and Zeynep Yilmaz performed the quality control, imputation, and meta-analysis of most of the cohorts of the anorexia nervosa genome-wide association study in chapter 3. Héléna Gaspar performed the gene-wise and pathway analysis. Julien Bryois conducted parts of the enrichment analysis. Zeynep Yilmaz calculated the polygenic scores. Paola Giusti-Rodríguez contributed the interactomics data. Jonathan Coleman conducted the neuroticism genome-wide association study, Kirstin Purves conducted the anxiety genome-wide association study, and Ken Hanscombe conducted the physical activity genome-wide association study. I contributed the conditional and joint analysis (COJO), the calculation of the genetic correlations, the partitioned heritability analysis, the multi-trait conditional and joint analysis (mtCOJO) the generalised summary data-based Mendelian randomisation analysis, the meta-analysis of the polygenic score analyses.

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1 Introduction

Eating is a universal human behavioural necessity for survival, and much of our social life revolves around food and communal eating[1]. Eating behaviour is scrutinized by others as an indicator of our health and mental state. Human eating behaviour, however, is distributed on a continuum[2] and like most human traits is partially heritable[3–5]. It has an underlying genetic component that acts in concert with environmental factors. For instance, appetitive traits in childhood, such as eating rate[6] and food fussiness[7], have reported heritabilities of 62% and 78%, respectively. Both traits show associations with body mass index[2] and disordered eating in later life[8], rendering them targets for preventive strategies for eating disorders and obesity.

Every continuum has extremes; and eating behaviour is no exception[9]. Both extreme overeating and undereating may be disordered and, if maintained, can be detrimental to health and well-being[10]. If an individual exhibits prolonged periods of disordered eating, they may have developed an eating disorder. Anorexia nervosa, bulimia nervosa, and binge-eating disorder are the three primary eating disorders that are recognised by current diagnostic schema[11]. Patients affected by these disorders display extreme forms of eating behaviour, such as calorie restriction, recurring binge eating, and compensatory behaviours[12], that can negatively affect an individual's health and health-related quality of life[13,14]. Eating disorders disrupt family functioning, represent serious health crises[15], and place a substantial financial burden on society[16].

Therefore, the goal of clinical psychology and medicine must be to identify risk factors that place individuals at the extremes of the eating behaviour spectrum and predispose them to the development of an eating disorder. Using this information to identify individuals at risk can then form the foundation of preventative strategies, while detecting risk factors may lead to the development of more effective treatments. Thus, the primary aim of this thesis is to improve our understanding of genetic and metabolic risk factors that contribute to the liability to anorexia nervosa while elucidating components of its aetiology and identifying potential causal risk factors. Work currently underway will enable the application of the methods described here to the study of the other eating disorders.

1.1 Anorexia nervosa

Anorexia nervosa is a severe eating disorder that is listed under Feeding and Eating Disorders in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM–5, **Box 1**) and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10)[11,17]. In 1868, William Gull wrote and read a paper on a condition comparable to anorexia nervosa in Oxford; concurrently, in 1873, both Gull in the United Kingdom and Ernest-Charles Lasègue in France published the first papers on anorexia nervosa[18,19]. Historical records of syndromes in saints akin to anorexia nervosa, such as Catherine of Siena[20], date back to ~1370.

Box 1. Diagnostic criteria for anorexia nervosa according to Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM–5)[11]

A) Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected.
B) Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.
C) Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.

Specify whether:

(F50.01) **Restricting type**: During the last 3 months, the individual has not engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas). This subtype describes presentations in which weight loss is accomplished primarily through dieting, fasting, and/or excessive exercise.

(F50.02) **Binge-eating/purging type**: During the last 3 months, the individual has engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

Specify if:

In **partial remission**: After full criteria for anorexia nervosa were previously met, Criterion A (low body weight) has not been met for a sustained period, but either Criterion B (intense fear of gaining weight or becoming fat or behavior that interferes with weight gain) or Criterion C (disturbances in self-perception of weight and shape) is still met.

In **full remission:** After full criteria for anorexia nervosa were previously met, none of the criteria have been met for a sustained period of time.

Specify current **severity**:
The minimum level of severity is based, for adults, on current body mass index (BMI); for children and adolescents, corresponding BMI percentiles should be used.

- Mild: BMI ≥ 17 kg/m^2
- Moderate: BMI 16–16.99 kg/m^2
- Severe: BMI 15–15.99 kg/m^2
- Extreme: BMI < 15 kg/m^2

Patients suffering from anorexia nervosa exhibit a characteristic phenotype with extremely low and life-threatening body weight during the acute phases of the disorder[11]. They maintain this low body weight through behaviours that counteract calorie consumption like fasting[21], excessive exercise[22,23], and purging, such as laxative, diuretic, amphetamine, thyroid hormone, or enema abuse, and self-induced vomiting[12,24,25]. Based on these behaviours, the current diagnostic schema differentiate between two subtypes: a restricting subtype when patients do not engage in compensatory behaviours, and a binge-eating/purging subtype when patients either engage in binge-eating behaviour, or the aforementioned purging behaviours, or a combination of both[11].

Eating disorder-related cognitions are common and a main feature of this complex psychiatric disorder[26]. Some patients experience body dysmorphia—namely a distorted perception of one's own body or body parts[27–33]—and report strong negative cognitive bias towards specific food items or macronutrients, especially fat. Some patients describe an intense fear of gaining weight[34] and overvalue weight and shape[26] in determining their own self-worth[35].

In the past, mainly societal factors such as the Western thinness ideal and the resulting psychological pressure were investigated as potential causal factors[36] because they were considered to influence the development of eating disorders around puberty. However, the paradigm has changed and, in recent years, researchers have made use of biologically-informed approaches to elucidate the aetiology of anorexia nervosa, incorporating biological factors into a multifactorial model of disorder onset[37–39]. However, our understanding of anorexia nervosa remains incomplete and many relevant questions about the disorder remain to be answered.

1.2 Epidemiology

Anorexia nervosa as a psychiatric disorder is more prevalent than was assumed during the last two decades. Its lifetime prevalence was traditionally estimated to lie between 0.2 to 1.0%[40–46], but studies published from 2013 to 2018 report higher prevalences of about 3.0% in community samples due to improved screening procedures in epidemiological studies and extended follow-up periods[47–49]. Incidence rates for anorexia nervosa range from 12.6 per 100,000 person-years in Danish inpatient settings[50], over 47.5 per 100,000 persons in British primary care settings[51], to 205.9 cases per 100,000 persons in the peak 14–15-year-old age category in Swedish registers[52]. At this peak age of detection, incidence of anorexia nervosa was 205.9 cases per 100,000 persons in females and 12.8 cases per 100,000 persons in males in Sweden in 2009. Incidence rates for anorexia nervosa are reported to be stable from 1995 until 2010 in Denmark[50] as well as in the United Kingdom from 2000 until 2009[51], but have increased in Sweden from 1995 until 2010[52], which probably reflects increased national register coverage as well as better clinical detection.

Anorexia nervosa shows a clear sex bias, with nine females affected for each male case[50,52–54]. This sex ratio is as high as 15:1 in Swedish patient register studies[55,56], making sex one of the strongest and most robustly replicated risk factor for anorexia nervosa[57–59]. However, Swedish patient registers only capture treatment-seeking individuals, which potentially overestimates the sex bias as only about 30-50% of individuals affected by anorexia nervosa enter health care services[60,61], with estimates for the percentage of males seeking treatment being unavailable.

1.2.1 Current diagnostic practices and challenges

The current primary diagnoses of all three primary eating disorders—anorexia nervosa, bulimia nervosa, and binge-eating disorder—changed in 2013 with the introduction of the DSM-5[42,44,49,62], which aimed to optimise classification and reduce the number of patients that were diagnosed with an eating disorder not otherwise specified (EDNOS). This category was generally used for patients who did not fully satisfy diagnostic criteria for either anorexia nervosa or bulimia nervosa.

Before the introduction of the DSM-5, amenorrhea (i.e., the absence of menstruation) was a required diagnostic criterion. However, up to 40% of patients with anorexia nervosa still menstruate[63], hence, the criterion was dropped[64]. The presence of primary or secondary amenorrhea is associated with increased severity of anorexia nervosa, potentially resulting in reduced fecundity[65], but also lower rates of sex hormone-related cancers like breast cancer presumably due to reduced lifetime exposure to estrogen[66,67].

The update of the diagnostic criteria improved the diagnostic process[42,62], but is still suboptimal as some patients are too complicated to classify. These patients fall under the renamed and extended category other specified feeding and eating disorders (OSFED) that includes subsyndromal forms of anorexia nervosa—called atypical anorexia nervosa—used for patients who do not fulfil all diagnostic criteria. For instance, their body mass index is not deemed low enough compared to age- and sex-specific normative values to diagnose them with the full syndrome of anorexia nervosa, or their binge-eating or purging behaviour does not occur in a high enough frequency[68].

Another factor that complicates the diagnostic process in eating disorders is that crossover between eating disorder diagnosis often occurs[69–75]. The description of crossover between eating disorders challenges the validity of current diagnostic schemata and, hence, a dimensional diagnostic approach has been forwarded akin the one applied in autism spectrum disorder[76–78].

1.2.2 Mortality, prognosis, and treatment

Anorexia nervosa is associated with elevated mortality compared with the general population. Reported standardised mortality ratios[40,43,79–83] range from 5.2 to 5.9. Compared with other psychiatric disorders, anorexia nervosa has one of the highest mortality rates[84]. Mortality ratios attributable to suicides are 18.1 contributing to its excess mortality[55,81,85]. Male cases show comparable mortality ratios of 4.1[86] and mortality in anorexia nervosa is higher in cases with comorbid psychiatric disorders[83].

Recovery from anorexia nervosa is possible. Up to two thirds of individuals with anorexia nervosa recover[87], but larger meta-analyses resulted in more conservative estimates stating that full recovery occurs in less than half of individuals with anorexia nervosa, 33% partially recover, and about 20% chronify[88,89]. Core symptoms are more likely to improve as about 60% of individuals with anorexia nervosa regain their weight and 57% begin to menstruate or menstruate again. However, the eating behaviour of only 47% of patients approaches that of healthy controls[88]. It is difficult to compare recovery across studies because the eating disorder research community has not adopted standardised criteria for recovery[90–93].

Renourishment is an essential first step in the treatment of anorexia nervosa[94,95]. Psychotherapy is effective for the treatment of anorexia nervosa in adults and adolescents[95–97], but no pharmacotherapeutic treatment is approved. For children and adolescents, family-based approaches are the most promising form of psychotherapy[98], whereas no talking therapy shows a clear advantage in adults[97]. In some cases, antidepressants and antipsychotics are used off-label to treat anorexia nervosa[99]. Based on these, a medication trial of olanzapine shows that antipsychotic treatment has a small effect on weight gain but less on the psychological symptoms[100]. Acknowledging the high mortality rate in conjunction

with the poor treatment options, it is imperative to improve health care for individuals affected by anorexia nervosa.

1.3 Risk factors for anorexia nervosa

Depending on the type of evidence demonstrating a relationship between a certain measurable construct, biomarker, or characteristic and the outcome of interest one can differentiate correlates, risk factors, and causal risk factors[101–103]. Every measured association between two variables is a correlation. By adding a temporal component and measuring the longitudinal association between variable X (i.e., the exposure) and the variable Y (i.e., the outcome), one can identify a potential risk or protective factor that may increase or decrease the subsequent risk to be affected by or develop the outcome.

If two group sampling is possible, conditions can be manipulated, and one group can be experimentally exposed to the risk factor while the other group remains unexposed. This experiment would have the ability to identify a causal risk factor[102]. However, such experiments are expensive and often not feasible due to ethical concerns. In modern epidemiology, statistical causal inference techniques can facilitate the identification of potential causal risk factors through hypothetically exposing individuals to risk factors by using instrumental variables that imitate the exposure by proxy. This approach is used in Mendelian randomisation (for a detailed description of the method, see Methods section of **chapter 5**).

Whereas myriad cross-sectional correlates have been identified, longitudinal research on risk factors in anorexia nervosa is relatively rare. Common alternative study types, including retrospective case-control studies, are weakened by potential recall bias, especially if exposures in early childhood are investigated[104]. The interpretation of results from studies on individuals who have recovered from anorexia nervosa is complicated due to the fact that recovery is ill-defined with no standardised criteria[90–92]. Additionally, it is impossible to differentiate whether a symptom that persisted after recovery is a "scar" due to the disorder itself or a trait that was present prior to disorder onset. These complications render the findings based on recovery research inconclusive

although they are useful for the generation of new hypotheses. Since the early 2000s, researchers have exploited longitudinal data sets to better understand disorder aetiology. My introductory review is focused on identified risk factors that represent exposures preceding the onset of anorexia nervosa. Additionally, comorbidity that shows aetiological overlap with anorexia nervosa is synthesised.

Anorexia nervosa can affect individuals from every walk of life independent of sex[44,52,105], sexual orientation[106–108], ancestry[109–111], and age[47,112], but certain characteristics or factors increase the likelihood of developing anorexia nervosa.

1.3.1 Ancestry, migration, and geography

Using Scandinavian register data, differences in risk of developing anorexia nervosa between children born to Swedish parents and children born to Middle Eastern or African parents are observed. On average the latter show a 60% lower risk of developing anorexia nervosa during their lifetime[57]. In a study that examines all immigrants jointly, both children born to first- and second-generation immigrants had lower risk for anorexia nervosa[113]. However, extending the investigation to second generation immigrants with a native-born mother and a foreign-born father shows elevated risk for anorexia nervosa but only in Denmark[113]. Detection of cases and awareness of the disorders differing by migration background are forwarded as potential explanations. Otherwise, anorexia nervosa is prevalent worldwide[111,114–116], indicating that the occurrence of anorexia nervosa is largely independent of ancestry[117].

1.3.2 Perinatal factors

The human perinatal period ranges from the 20th–28th gestational week until four weeks after birth. Syntheses of older studies show mixed findings, suggesting that individuals who experience obstetric complications such as birth traumata may be more likely to develop anorexia nervosa later in their life (**Box 2**)[118,119].

Box 2. Perinatal factors potentially associated with the development of anorexia nervosa

Pregnancy-related maternal or paternal factors

- Maternal anemia[120]
- Pre-eclampsia[120]
- Maternal diabetes[120]
- Older father (confounded by higher education)[121]
- Shorter maternal smoking duration (confounded by maternal characteristics)[121]

Birth characteristics

- Prematurity: born during weeks 23–32[121,122]
- Twin or triplet birth[121]
- Placental infarctions[120]

Newborn characteristics

- Neonatal hyporeactivity/hypotonia[120]
- Tremors[120]
- Hypothermia[120]
- Oxygen need[120]
- Birth weight[123]

Three studies evaluate data from the Swedish population[57,58,124], one study focuses on two Italian samples[120], one on a British birth cohort[59], and one on a Norwegian birth cohort[123]. In the Italian study, neonatal hypotonia, hypothermia, and oxygen need are associated with anorexia nervosa[120]. However, the APGAR score at five minutes (i.e., appearance, pulse, grimace, activity, and respiration) that captures these features in newborns shortly after birth is not associated with anorexia nervosa in the larger Swedish register study[58]. The British and Norwegian studies do not find associations between birth characteristics reported by Favaro et al. and lifetime anorexia nervosa[59,123]. In contrast to the Italian study that investigates health records from one hospital, these larger population-based studies are less limited by selection bias, lending greater confidence in their findings.

1.3.3 Family characteristics including socioeconomic status

Studies of socioeconomic status subcomponents—educational attainment and income—indicate that higher maternal and paternal education is associated with anorexia nervosa in progeny[57,121] whereas higher parental income is not associated with anorexia nervosa[121]. This phenotypic relationship is reflected in a relatively strong observed positive genetic correlation between anorexia nervosa and educational attainment (r_g = 0.34)[125]. It may indicate that individuals with anorexia nervosa are more likely to carry genetic variants that predispose them to higher educational attainment.

1.3.4 Body composition

Extreme underweight is a key characteristic of anorexia nervosa and part of its diagnostic classification. The combination of restrictive eating (i.e., fasting) and compensatory behaviours leads, on average, to a loss of approximately 50% of fat mass in affected females and males[126–128]. However, other body compartments, including fat-free and bone mineral mass, are also compromised by the disorder. Osteopenia and osteoporosis are common in patients with anorexia nervosa[129–131], increasing the risk for fractures[131]. Low bone mineral mass may persist after recovery[126,132,133]. Furthermore, using data from the Avon Longitudinal Study of Parents and Children (ALSPAC), prospectively modelled body mass index trajectories are associated with later eating disorder diagnoses in adolescence: Girls who go on to develop anorexia nervosa show a significantly lower growth curve compared with healthy controls or other eating disorder patients. Comparing later cases of anorexia with those who do not develop an eating disorder, the difference between girls becomes visible at the age of four and for boys at the age of two years[134]. This indicates an alteration in body composition before the onset of the full syndrome as defined by DSM-5 or ICD-10.

1.3.5 Physical activity

Some individuals with anorexia nervosa tend to use excessive exercise as a weight control behaviour[23]. In anorexia nervosa, most research on physical activity focuses on self-report or clinical observations, but few studies use objective measures such as accelerometers. A meta-analysis on objectively measured physical activity published in 2015 suggests higher levels of physical activity in anorexia nervosa that may be associated with more severe psychopathology[22].

In research on physical activity, the measurement method is crucial. Assessing patients simultaneously with exercise questionnaires and accelerometers reveals a problematic mismatch between subjective and objective measurements. Patients with anorexia nervosa self-report higher physical activity than objectively measured by accelerometers. However, objectively obtained physical activity does not differ between anorexia cases and controls, indicating reporting bias[135]. Moreover, it may depend on the type of physical activity assessed as individuals with anorexia nervosa appear to most often engage in "fidgeting". (A type of non-exercise physical activity that can be measured by shoe-based accelerometers[136]). However, findings regarding fidgeting are mixed and study results may be influenced by participant compliance as the accelerometers used had several leads and wires attached[137]. This mixed picture is further confirmed by reports that individuals with anorexia nervosa may spend more time engaging in light intensity physical activity than controls[138], and studies that report less high intensity physical activity in anorexia nervosa than in controls[138,139].

In summary, individuals with anorexia nervosa self-report higher physical activity and observations in health care settings add further evidence. However, the current body of evidence using objective measurement methods is inconclusive and no longitudinal studies have yet been performed, indicating a gap in the literature.

1.3.6 Eating behaviour

Individuals with anorexia nervosa often restrict their food intake below healthy levels and alter the macronutrient composition of their food. Community-dwelling individuals with anorexia nervosa self-report that they consume less fat[140]. This has been confirmed in laboratory studies[21] in which individuals with

anorexia nervosa overall consume fewer calories than controls[141]. Similarly, individuals with anorexia nervosa consume food with lower energy density (the number of calories per gram of food) than unaffected controls[142,143]. Individuals with anorexia nervosa also report a fear of fat and often avoid its consumption[21]. However, the construct of "fat phobia" has been criticised as being a "Western misinterpretation" of general food aversion[144]. Even after treatment during which individuals with anorexia nervosa gain weight and their psychological symptoms improve, they show eating patterns comparable to those before treatment[142,145,146]. Overall, lower diversity and energy density of chosen food items in anorexia nervosa are associated with poorer outcome[143,147].

Laboratory food consumption studies suggest that calorie intake in anorexia nervosa is associated with anxiety levels shortly before food intake[148] and with the type and calorie density of a potential preload (i.e., a premeal consumed before the actual meal)[149]. It has been hypothesised that starvation may have an anxiolytic function in anorexia nervosa[34]. The laboratory observation of an association between anxiety level and food consumption provides evidence for this assumption. Further, individuals affected by anorexia nervosa tend to consume more protein after a preload independent from its calorie content[149], raising the question whether appetite-moderating mechanisms are dysregulated only during acute episodes or if this type of consumption is a trait in individuals with anorexia nervosa.

From a developmental perspective, it is unclear at what stage of life individuals who will be affected by anorexia nervosa begin to change their eating behaviour. Reductions in food intake may commence in early childhood. Again, taking advantage of data from the ALSPAC, we modelled parent-reported eating behaviour longitudinally and estimated its association with eating disorder diagnoses in adolescence. We found that parent-reported persistent undereating from 1.3 to 9 years was associated with higher risk for anorexia nervosa at age 16 years[8], suggesting some prodromal change in eating behaviour before disorder onset.

1.3.7 Dieting and fasting

In lay terms, dieting describes the attempt to reduce or the successful reduction of calorie intake either to maintain or lose weight. Dieting has been forwarded as a risk factor for anorexia nervosa and is commonly regarded as one[150]. However, this hypothesis is questionable. Dieting is common in the general population with more than 50% of females between the ages of 35 and 65 years and more than 30% of males between the ages of 45 and 65 reporting dieting behaviour[151,152]. Between the ages of 13 and 16 years, more than 10% of female adolescents self-report dieting a couple of times[151]. However, not everyone who diets goes on to develop an eating disorder.

The evidence base for the involvement of dieting or fasting in anorexia nervosa is weak[103] as only a few studies investigated the relationship longitudinally. These studies are, furthermore, limited by the narrow age range of their participants as they sampled adolescents from age 11 years onwards. Dieting behaviour starting at this point in time could reflect early symptoms of an eating disorder complicating the delineation between disorder onset and classification as a risk factor[103]. One longitudinal investigation using data from the National Heart, Lung, and Blood Institute Growth and Health Study illustrates that individuals who go on to develop anorexia nervosa self-report their eating behaviour as comparable to unaffected controls until one year before self-reported disorder onset. Then, they start to consume fewer calories and concurrently change their dietary patterns, consuming less fat[153]. However, the cohort of 991 White girls included only 14 individuals who developed anorexia nervosa, limiting the generalisability of these findings.

1.4 Genetics of complex traits

Nearly every common human trait is partially heritable and also influenced by environmental factors[154]. This is important for research that uses inferential statistical methods as it suggests that neither purely genetic nor purely environmental models will be able to explain 100% of variance in any trait. **Box 3** presents the components of variance measured by models used in quantitative genetics to better understand disorder biology.

Box 3. The definition of broad-sense and narrow-sense heritability[155]

Phenotypic variation (V_P) is the "observed variation in a particular trait" in a population at a certain time point[156–158].

Heritability is "formally defined as the proportion of phenotypic variation (V_P) that is due to variation in genetic values (V_G)"[156–158]. Heritability is an estimate of a population parameter that is dependent on time point of measurement and the environment[158].

Genetic values (V_G) describe the combination of "the effects of all genetic loci, including possible allelic interactions within genetic loci (i.e., dominance) and between genetic loci (i.e., epistasis). This value creates genetic variation in a population when it varies between individuals"[156–158].

Broad-sense heritability, "defined as $H^2 = V_G/V_P$, captures the proportion of phenotypic variation due to genetic values that may include effects due to dominance and epistasis"[156–158].

Narrow-sense heritability, $h^2 = V_A/V_P$, captures only that proportion of genetic variation that is due to additive genetic values (V_A)"[156–158].

As nearly every human trait is partially explained by genetic values (representing the sum of the effects of genetic variants genome-wide), the next logical step is to identify genomic variants that are associated with these traits.

1.4.1 Structural properties of the human genome

Over the last two decades, several genome-wide association studies have reported and robustly replicated associations between genomic regions (i.e., loci on chromosomes) and phenotypes[159,160] exploiting small DNA sequence variants for statistical analyses. These DNA variants include single nucleotide polymorphisms (SNPs) or insertion-deletion variants of one or more nucleotide (indels) across the whole genome. These genome-wide association studies

profoundly changed the perception of heritable contributions to complex human traits[161]. We know now that the heritable component of complex human traits in psychiatry is attributable to probably more than 1,000 polymorphisms in the human genome that each carry relatively small effect sizes and act in concert[162,163]. Genome-wide association studies exploit structural properties of the human genome, including chromosomes, alleles, linkage disequilibrium, and haplotype blocks (**Box 4**).

Box 4. Structural properties of the human genome

Chromosomes are an organisational unit in the human genome. Humans carry 22 chromosomes of which 21 are autosomes that are equal between females and males and one sex chromosome either X or Y. In most cases, females carry two X chromosomes while males carry one X and one Y chromosome. Chromosomes are of different length with chromosome 1 being the longest. Chromosomes are generally shorter with increasing number[164].

Polymorphisms are small changes in the sequence of the DNA nucleotides: adenine (A), cytosine (C), guanine (G), thymine (T). For instance, at a certain **locus** the nucleotide A is replaced with T through mutation. This replacement is called a single nucleotide polymorphism (**SNP**). If one or more nucleotides are inserted or deleted in a certain chromosomal segment, it is called an inversion or deletion (i.e., **indel**). Polymorphisms can be inherited or occur *de novo* during gamete formation (i.e., egg or sperm cell formation)[165].

Allele is a specific variant of a polymorphism. Humans are diploid, meaning that they have two alleles per polymorphism, although genetic variants frequently have more than two alleles when considered on a population basis. Each allele is either inherited from the father or the mother.

Allele frequency describes the frequency with which the alleles occur in the general population. These allele frequencies build the basis for association testing. For instance, in case-control settings, logistic regression compares the allele frequencies of a certain allele between cases and controls[166].

Linkage disequilibrium describes the phenomenon throughout the human genome that alleles are not independent from each other. It stands in contrast to Mendel's Law of Independent Assortment that states that the inheritance of one pair of factors (genes) is independent of the inheritance of the other pair. Pictorially, it is a pattern of geographic subdivision of a chromosome: Going along a chromosomal strand, it is, therefore, possible to predict the following nucleotide based on the preceding (except at recombination hotspots). Different measures to quantify the association between pairwise nucleotides along a chromosomal strand exist, including D, D', and r^2 which are dependent on the allele frequencies[167,168].

A **haplotype** block defines a region of high linkage disequilibrium on a chromosome, meaning that the identities of nucleotides in this region are highly correlated with each other. In humans, haplotypes are of different length between few kilobases (kb) to >100 kb and differentially distributed along the chromosomes. A myriad mechanisms contribute to the emergence of haplotypes in humans: recombination during meiosis, natural selection, mutation, genetic drift, population division, changes in population size (i.e., bottlenecks), exchange of individuals among populations, inbreeding between individuals of the same population, and genomic inversions[167,168].

1.4.2 Genome-wide association studies

Genome-wide association studies capitalise on this organisational structure of the human genome. They assess polymorphisms in study participants that then are associated with phenotypes. The genomic data for genome-wide association studies are generated with the help of microarrays during a process that is called genotyping[161]. During genotyping, the polymorphisms that are present in an individual's genome are measured. The microarray (i.e., genotyping chip), which is a postage stamp-sized (or smaller) glass slide coated with thousands to millions of

short DNA sequences (i.e., probes), is washed/covered with a buffer that contains the participant's fragmented DNA. If DNA polymorphisms are present both in the participant's genome and also on the genotyping chip, the participant's DNA fragments bind (i.e., hybridise) to the probes on the genotyping chip. Following binding, a chemical reaction elicits a fluorescent signal that can be read out by a computer and is assigned to a certain SNP on the human genome, because the probes are on certain positions on the genotyping chip. The genotyping chip carries probes for both versions of an allele to indicate if an individual is homozygous (e.g., carries the same allele of a polymorphism twice) or heterozygous (e.g., carries two different alleles of the polymorphism)[169].

After genotyping, the raw genotyping data must go through a quality control process that follows best practice. For instance, polymorphisms that are measured (i.e., called) in less than 99% of the participants (i.e., that have high SNP missingness) are excluded from the analysis. Similarly, participants for whom less than 95% of genetic variants could be called are excluded from the analysis[170].

The content of microarrays is typically based on the linkage disequilibrium between polymorphisms, which means it is only necessary to measure one index polymorphism in a haplotype block (which can be thought of as a set of variants that have medium to high correlation [i.e. linkage disequilibrium] with each other). This index polymorphism would, ideally, be in linkage disequilibrium (e.g., $r^2 > 0.75$) with its neighbouring polymorphisms in which case it *tags* these genomic variants sufficiently. However, *tagging* of genomic variants that are in linkage disequilibrium comes at a cost. For instance, statistical power is proportional to the r^2 of any given tagging variant with a causal polymorphism. This means if one needed 4,000 participants to detect a causal variant that were directly genotyped (e.g., present on the genotyping chip) or in perfect linkage disequilibrium, one would need to increase the sample size by $4{,}000 * 1/0.80 = 1000$ to identify a causal variant in $r^2 = 0.80$ with the tagging SNP[168]. This tagging method reduces the number of polymorphisms that must be genotyped in participants to capture the whole genome and can lower study costs. Currently available genome-wide genotyping chips only assess up to five million polymorphisms (i.e., markers), including SNPs and indels, and the most commonly used arrays have between 400,000 and 700,000 tagging variants. Costs for

genotyping are typically below 30 pounds per sample. However, decreasing costs for whole genome sequencing mean that genotyping may eventually be replaced by sequencing[171].

In 2002, the International HapMap Project was founded which genotyped one million polymorphisms in 269 individuals of European, Han Chinese, Japanese, and Yoruban ancestry. The number of polymorphisms was later updated to 3.1 million. Not only did the International HapMap Project genotype individuals, it also determined haplotype blocks and, hence, the patterns of linkage disequilibrium across the genome. The consortium created a geographical map of haplotypes in the human genome. With this knowledge, genotyping microarrays could be designed such that they tag about 96% of the polymorphisms present in Europeans[172]. Moreover, the project provided the theoretical basis for the genome-wide significance threshold of 5×10^{-8} that is conventionally applied in genome-wide association studies to adjust for the approximate number of independent tests that are performed[173].

A genome-wide association study represents a regression analysis at each polymorphism to test for an association between the phenotype and the genotype. The genotypes (e.g., SNPs or indels) are associated with a trait, if carrying a certain variant is associated with a higher value on a continuous trait such as body mass index or if individuals with a disorder such as anorexia nervosa carry this variant at a higher frequency than controls. The primary way to exploit tagging to increase the coverage across the whole genome is to impute polymorphisms that have not been directly genotyped. This is done with the help of of densely genotyped or sequenced reference panels[174] and means that >7 million variants can typically be tested for association. Thus, after imputation, for each polymorphism, genome-wide association studies typically fit either a linear regression for continuous outcomes or a logistic regression for binary outcomes[161].

1.4.3 Relatedness and population structure

Population structure and family or cryptic relatedness are serious problems in genome-wide association studies and can confound results leading to spurious associations (i.e., false positives)[175] by altering allele frequencies in a study sample[176,177]. Family or population structure is present in a data set of genotypes if certain polymorphisms occur more often than expected, unrelated to the studied trait[178].

Genetic drift describes the random drift of certain alleles at higher or lower frequencies in smaller populations, over generations. Such changes in allele frequencies are stochastic and not due to selection but instead are due to chance events[179] (**Box 5**). Additionally, individuals who live geographically closer together tend to mate with each other, which can also lead to enrichment of certain alleles in certain genomic regions[180,181].

Box 5. Genetic phenomena that lead to changes in allele frequencies[178,182]

Family structure describes structure within the sample due to familial relatedness among samples.

Cryptic relatedness describes structure within the sample due to distant relatedness among samples with unknown family relationships.

Population structure describes structure within the sample due to differences in genetic ancestry among samples.

Genetic drift summarises random fluctuations in allele frequencies over time due to sampling effects, particularly in small populations.

Genetic drift can confound case-control studies if cases and controls are poorly matched for ancestry[183]. In this case, genetic drift drives what is termed as "population stratification" where many variants in the genome have alleles that occur more often in cases than in controls but are unrelated to the phenotype (i.e., false-positive associations).

Therefore, methods to account for population stratification must be employed in analyses. Two approaches can be taken. First, adjustments can be done via the inclusion of principal components as covariates that represent the underlying population structure[180]. These ancestry principal components are calculated on a pruned set of the genotype data in unrelated (i.e., distantly related) participants after quality control. Alternatively, relatedness can be inferred from the calculation of a genetic relatedness matrix (GRM), that is a genotypic covariance matrix that represents pairwise estimates of genomic relatedness between each participant in the whole sample[184]. After calculation, the ancestry principal components and/or the genetic relatedness matrix are included as covariates in the regression models[185].

1.4.4 Heritability estimation using linkage disequilibrium score regression

Narrow-sense heritability can be estimated at its lower bound using linkage disequilibrium score regression in a computationally efficient way[186]. Linkage disequilibrium score regression only requires summary statistics from genome-wide association studies. Linkage disequilibrium score regression exploits the relationship between markers that tag other polymorphisms in linkage disequilibrium and expected genome-wide association test statistics. It regresses the test statistics on the linkage disequilibrium scores of each marker. The linkage disequilibrium score is "the sum of linkage disequilibrium r^2 measured with all other single nucleotide polymorphisms"[187]. In other words, linkage disequilibrium score expresses with how many other polymorphisms the index marker is in high linkage disequilibrium. The model assumes that larger regions of linkage disequilibrium which have fewer but longer range haplotypes are more likely to harbour causal variants. This means that polymorphisms with high linkage disequilibrium are more likely to tag a causal variant on any chromosome.

In a linkage disequilibrium regression, the regression slope represents a conservative estimate of the narrow-sense heritability. Simulations show that the method is robust to familial environmental confounding[186]. The intercept (i.e., the point where the regression line crosses the Y axis) indicates if population structure or cryptic relatedness inflates the test statistics of the genome-wide association study if it is significantly greater than 1. However, simulations have shown that the

intercept is dependent on the sample size of the genome-wide association study and the true heritability of the trait, sometimes resulting in intercepts greater than 1 even though population structure and cryptic relatedness has been sufficiently controlled by including ancestry principal components[188]. Nevertheless, linkage disequilibrium score regression gives heritability estimates that are valid in most situations, although they are a "worst-case" estimate as they only capture the effect of common variants in high linkage disequilibrium.

1.4.5 Genetic correlations

Genetic correlations are estimates of the genetic overlap between two traits[189]. An analytical extension of linkage disequilibrium score regression can be used to quantify the degree to which pleiotropic genomic variants or correlation between causal loci contribute to a pair of traits[190]. Accordingly, a negative genetic correlation indicates that the same genomic variants tend to have alleles that are associated with both traits in opposite directions whereas a positive genetic correlation indicates that the same genomic variants have alleles that are associated with both traits in the same direction. Genetic correlations range between -1 and +1, but may be estimated at a value greater than 1 due to sampling variation. To estimate the genetic correlation, the effect size of trait 1 is multiplied with the effect size of trait 2 and then regressed on the linkage disequilibrium score of the corresponding polymorphism. The slope of the regression line indicates the genetic correlation between both traits.

1.4.6 Genetics of anorexia nervosa

Eating disorders are heritable traits and research spanning a variety of genetic epidemiologic methods over the past 40 years has demonstrated this repeatedly. In European populations, family[191–194] and twin studies show that anorexia nervosa is heritable with estimates ranging between 32 to 74%[38,195], meaning that a substantial degree of trait variance is explained by heritable factors. Most twin studies, however, have been performed on small samples with low numbers of anorexia nervosa cases, limiting statistical power and resulting in considerable uncertainty of the estimates. Heritability estimates of anorexia nervosa depend on the symptom constellation: Defining anorexia nervosa more

stringently by including the amenorrhea criterion, for example, yields higher twin heritability estimates, indicating that narrowly-defined anorexia nervosa is more heritable than the broadly-defined syndrome[196].

Three genome-wide association studies of anorexia nervosa have been performed[125,197,198]. The first two[197,198] are small with about 3,000 cases and 15,000 controls and identified no genome-wide significant loci. Boraska et al.[197] shows greater than chance convergence of direction of effects between the discovery and the replication sample, indicating evidence for a polygenic signal that could be detected with more statistical power.

With increased sample size, the initial reported genetic correlations of anorexia nervosa with body mass index (SNP-r_g = -0.18, SE = 0.04, p = 3 x 10^{-7}) and schizophrenia (SNP-r_g = 0.19, SE = 0.04, p = 3 x 10^{-5}) emerged[190]. In 2017, the genome-wide association study by Duncan et al. identified the first genome-wide significant locus on chromosome 12 that has also been implicated in autoimmune diseases, including type 1 diabetes and inflammatory bowel disease[125].

1.4.7 Epigenetics in anorexia nervosa

Epigenetic factors are modifications of the DNA or the proteins that bind DNA that do not change its sequence and can regulate gene activity. Environmental factors are associated with these epigenetic modifications[199]. Anorexia nervosa is associated with several factors that make the involvement of epigenetic factors likely, such as female preponderance, peak age of onset during puberty, and reports of monozygotic twins discordant for anorexia nervosa[200,201]. Research on epigenetics in anorexia nervosa is in its infancy and has exclusively focused on methylation profiles. A few differentially methylated regions in the genome are identified; however, none is robustly replicated as the studies in general are of poor quality[39]. For a full review, see **Appendix 1**.

1.4.8. Sex differences in genetics

Humans carry a complex system comprised of several components that influence differences between the sexes, including sex chromosomes, sex hormones, and sex-dependent gene expression[202]. Sex chromosomes contribute genetically to these differences. Human sex chromosomes have pseudo-autosomal regions. These regions on Y have an analogue on X and, hence, the same properties as autosomes (i.e., they have partial biallelic expression). In females, one of both X chromosomes is partially deactivated[203], meaning that parts of the second X chromosome are not translated into proteins[204]. Sometimes the maternal X chromosome is inactivated, while in other cases it is the paternal X chromosome; thus, in certain human cells, different alleles influence X chromosomal gene expression[205,206]. Due to these properties, the X chromosome is difficult to analyse and many genome-wide association studies are lacking analyses of X, which inevitably misses genetic variants that contribute to trait heritability[202].

The definition of environmental factors is complicated as most traits are partially heritable[154]. In the quantitative additive genetic model, biological sex and the related hormonal changes during the lifespan are seen as environmental factors: Puberty and menopause are sensitive periods in which sex hormone concentrations and an individual's liability for illness change, resulting in increased incidence rates. This sensitive period is also observed in anorexia nervosa[52].

Box 6. Genetic architecture

The **genetic architecture** of a trait comprises all different heritable components that contribute to its variance. These components can be common DNA polymorphisms that occur at more than 1% in the population, rare DNA variants, and copy number variants that are by definition larger than 200 kb, and their potential interactions[207].

Association studies can investigate if the genetic architecture of a trait differs between females and males (**Box 6**). A genome-wide association study comparing common variants with minor allele frequencies above 5% between females and males (n=114,863) indexes no genomic loci that are directly

associated with biological sex[208]. This has methodological implications for genome-wide association studies of phenotypes that primarily affect females like anorexia nervosa and breast cancer such that they can include male controls to boost their sample size and statistical power[202].

The overall heritability of most traits is the same or very similar between females and males [209,210], suggesting that the same inherited factors contribute to trait variance in either females or males. A few studies, however, show significant deviations from perfect genetic correlations (i.e., $r_g = 1$) between males and females[211,212], meaning that the inherited factors that contribute to trait variance in either females or males are not necessarily the same. These traits are mostly body composition traits, such as body fat percentage, absolute fat mass, and its proxy measure body mass index[213–215]. Genome-wide studies associate genomic loci with these traits only in females or identify significantly stronger effects in females than in males for a certain locus.

These sex-dependent effects are mediated by gene expression[216]. Gene expression, however, is dependent on additional factors, including the developmental stage of the organism, age, tissue type, and environmental conditions[217]. A ground-breaking study demonstrated that sex-biased genetics are present in five species: humans, macaques, mice, rats, and dogs. Approximately 13% of genes are differentially expressed between females and males of which about 23% genes show a conserved (i.e., species-shared) sex bias and 77% are species-specific. This suggests that sex bias occurred more recently during evolution and, thus, molecular sex differences observed in humans may not translate to other nonhuman mammals[218], which must be taken into account when animal studies model human sex differences. Although the sex bias of most genes is tissue-specific, about 562 conserved sex-biased genes are sex-biased in more than one tissue and, depending on tissue type, 85-95% of genes with conserved sex-biased gene expression are located on autosomes. Which mechanisms lead to this sex bias in gene expression is unclear.

Biological sex is influenced by sex chromosomes, sex hormones, and sex-biased autosomal gene expression leading to sex differences in human biology. These sex differences may contribute to the higher liability for anorexia nervosa in females.

1.5. Comorbidity of anorexia nervosa

1.5.1 Anxiety

Up to 60% of individuals affected by an eating disorder report symptoms of anxiety cross-sectionally[219–225] and whether these cease after recovery is unclear as studies show mixed findings[226]. Anxiety symptoms are a prognostic marker for poor outcome of treatment[227]. For instance, social anxiety is present in up to 20% of anorexia nervosa patients[191] and is seen as a barrier to treatment[220], but levels of social anxiety are similar across all eating disorders diagnoses[228].

About 10% of individuals with anorexia nervosa present with a comorbid panic disorder[220] and especially paternal panic disorder increases risk for anorexia nervosa in the offspring by 129%[194]. Retrospective studies suggest anxiety symptoms and disorders as risk factors for anorexia nervosa[220,229] and, worrying at the age of 10 years is prospectively associated with an eating disorder diagnosis at ages 14 and 16 years which does not differ between the sexes[230]. Large longitudinal register studies demonstrate that social phobia and generalised anxiety disorder can precede anorexia nervosa[194]. However, a recent review of longitudinal studies synthesises mostly negative findings[231] suggesting that anxiety unlikely is a risk factor for anorexia nervosa which is supported by a Mendelian randomisation study[232]. However, the SNPs used as instrumental variables for the causal inference model are still relatively weakly associated with both traits which considerably limits the interpretability of the findings.

In the opposite direction, preceding eating disorders are longitudinally associated with higher risk for anxiety disorders[233]. The bidirectional relationship most probably suggests shared underlying factors elevating liability for both disorders concurrently. Bivariate twin studies corroborate these findings by confirming a genetic overlap between anorexia nervosa and generalised anxiety disorder[234,235] and between anorexia nervosa and anxiety sensitivity[236], suggesting that both phenotypes share heritable factors that contribute to their development. Lowest body mass index is associated with the overlap between both disorders[234], suggesting that body composition may mediate or moderate the relationship.

In summary, anxiety and anorexia nervosa are highly comorbid and share genetic variants influencing both traits and, therefore, increase the risk for the development of the former and the latter concurrently.

1.5.2 Obsessive-compulsive traits

Cross-sectionally, obsessive-compulsive traits are common in anorexia nervosa[221–224,237–240] but not exclusively as they are also observed in bulimia nervosa[239,241]. Obsessive-compulsive traits are a marker of poor treatment outcome in anorexia nervosa[242] and, for instance, impaired cognitive set shifting measured by the Wisconsin Card Sorting Task persists attenuated after recovery[243–245]. Cognitive inflexibility is a neuropsychological testable symptom that is common in obsessive-compulsive disorder.

Early family studies indicate shared familial factors between anorexia nervosa and obsessive-compulsive disorder[191]. Retrospective reports[220,246–248] and small longitudinal studies[249,250] suggest obsessive-compulsive disorder to be a risk factor for anorexia nervosa. However, they are limited by small sample sizes[249] and an average age of participants past the common onset of anorexia nervosa[250]. Large longitudinal register studies in Denmark and Sweden show that obsessive-compulsive disorder is a clear familial risk factor for anorexia nervosa with a four-fold higher risk to be diagnosed with anorexia nervosa after receiving a diagnosis of an obsessive-compulsive disorder and a two-fold risk to be diagnosed with anorexia nervosa if a first-degree relative was diagnosed with obsessive-compulsive disorder[194,251,252]. Moreover, the effect seems to work bidirectionally increasing risk for a diagnosis of obsessive-compulsive disorder after being diagnosed with anorexia nervosa[251].

Notably, both the data from the Swedish and the Danish registers show that obsessive-compulsive disorder is a stronger risk factor for males to be diagnosed with anorexia nervosa than for females as male sex doubles the risk[194,251]. An additional twin analysis of the Swedish sample confirms the familiality and shows a large genetic correlation between anorexia nervosa and obsessive-compulsive disorder (twin-r_a = 0.52, 95% CI: 0.26, 0.81)[251]. The genetic correlation (SNP-r_g = 0.52, SE = 0.12, p = 1.04 x 10^{-5}) is replicated by the Brainstorm Consortium[253] and a genetic cross-disorder analysis[254], using molecular genetic techniques and linkage disequilibrium score regression[190]. However, obsessive-compulsive traits, such as preference for symmetric patterns and concerns about dirt and germs, at the age of ten years were not longitudinally associated with an

eating disorder diagnosis in a British birth cohort[230], raising the question if the shared genetic liability may be age-dependent.

In summary, the relationship between anorexia nervosa and obsessive-compulsive disorder is bidirectional, both disorders share common genetic liability indexed by genetic correlations in twin and molecular genetic studies. Notably, obsessive-compulsive disorder is a sex-dependent risk factor increasing risk especially for males.

1.5.3 Affective traits

Affective symptoms are common in patients with anorexia nervosa[255–257], up to 60% of adolescents with anorexia nervosa report depressive symptoms[224,258,259] and major depressive disorder occurs comorbid with anorexia nervosa[260,261]. Clinical samples report higher levels of depressive symptoms than community-dwelling individuals[262] and a network analysis identifies depression as a central symptom in anorexia nervosa[263], but patients report that their depressive symptoms improve with treatment[264].

Longitudinally, depression is associated with subsequent anorexia nervosa[252,265] and in 1984 familial coaggregation of depression and anorexia nervosa was first described[266]. In a bivariate twin study, depression and anorexia nervosa correlate genetically (twin-r_a = 0.29), indicating shared genetic liability[267]. Anorexia nervosa is associated with higher rates of suicidality which is partially mediated or moderated by the relationship between anorexia nervosa and depression[55].

Anorexia nervosa and depression share risk factors; however, whether a bidirectional relationship exists is unclear. The shared genetic vulnerability may influence the risk for suicidality seen in anorexia nervosa.

1.5.4 Psychosis

Little attention has been placed on the relationship between eating disorders and psychosis. Interest in the association has increased after reporting of a significant positive SNP-based genetic correlation of r_g = 0.23 between schizophrenia and anorexia nervosa, indicating shared genetics between both traits[125,190,253]. Cross-sectionally, comorbid psychosis has been reported in

anorexia nervosa[258,268–271] and worldwide retrospective surveys show that a diagnosis of anorexia nervosa can precede psychotic experiences and increases the risk by 180% of being diagnosed with a psychosis-related disorder[272]. This finding is replicated in Swedish and Danish register studies showing that anorexia nervosa is associated with higher odds for schizophrenia (R. Zhang, personal communication). Additionally, a schizophrenia polygenic score that indexes one's personal propensity to schizophrenia[273] as well as psychotic experiences at age 13 years[274] are associated with disordered eating and binge-eating behaviour at age 18 years in the Avon Longitudinal Study of Parents and Children (ALSPAC). However, some of these associations may be moderated by depressive symptoms.

In summary, anorexia nervosa and schizophrenia coaggregate in families and are positively genetically correlated. This genetic overlap may contribute to certain symptoms of anorexia nervosa, like binge-eating behaviour.

1.5.5 Attention deficit hyperactivity disorder

The association between attention deficit hyperactivity disorder (ADHD) and anorexia nervosa is less clear. Most cross-sectional studies do not show an association between anorexia nervosa and ADHD[275,276]. Using Swedish register data, familial coaggregation of ADHD and anorexia nervosa is documented with no differences between the sexes. The familial analysis shows a genetic correlation of 0.14 between ADHD and anorexia nervosa[277], while molecular genetic correlations are nonsignificant[125,253]. Additionally, an ADHD polygenic score—indexing genetic liability for ADHD—is associated with drive for thinness and body dissatisfaction key symptoms of anorexia nervosa in the Child and Adolescent Twin Study in Sweden (CATSS)[277].

In summary, some evidence for an overlap between ADHD and anorexia nervosa symptoms exists, mainly with binge-eating and purging behaviour, but less so for restrictive behaviour with findings for a genetic overlap between ADHD and anorexia nervosa being inconclusive.

1.5.6 Autism spectrum

Autistic traits, including systemising[278], problems with mentalisation[279], and difficult social interactions[280,281], as well as autism spectrum disorder itself[282,283] are associated with anorexia nervosa[284]: About 23% of anorexia nervosa patients present with autistic symptoms; however, meta-analytic findings are limited by the fact that six of eight studies are performed on the same sample[285] and that the overall estimate is dependent on the applied diagnostic criteria and assessment methods. Parent-reported autistic symptoms during development do not match with autistic symptoms observed in acutely ill anorexia nervosa patients[283], suggesting that autistic traits in anorexia nervosa may develop during disorder onset. Some studies in children, however, show autistic traits in early onset eating disorders[286].

Early family studies suggest a familial component that is shared between autism and anorexia nervosa[287]; however, a large Danish register study demonstrates that this familial component is nonspecific and may also contribute to risk for developing other psychiatric disorders. This is corroborated by the fact that autism spectrum disorder and anorexia nervosa are not directly genetically correlated[125]. Therefore, autistic symptoms that develop during anorexia nervosa onset are more likely to present general symptoms of psychopathology[284,288]. A final judgement is difficult to make because most studies merely compare eating disorder patients with healthy controls but with no group of individuals affected by other psychiatric disorders. Furthermore, they only investigate small potentially selected samples[289]. However, it is important to note that autistic traits are associated with poorer outcome in anorexia nervosa[290–292].

Regarding sex differences, in Denmark, males with a history of anorexia nervosa are far more likely to be diagnosed with subsequent autism spectrum disorder than females (hazard ratio = 22.0 vs 12.8). The study, however, is unable to explain the phenomenon, but they hypothesis that disordered eating behaviour may be an early symptom of autism and individuals may firstly be misdiagnosed with an eating disorder until they receive the final diagnosis of autism spectrum disorder. The diagnostic problem may be alleviated with the introduction of the new diagnosis avoidant restrictive food intake disorder as individuals with autism spectrum symptoms might fall under this diagnosis. The sex difference is unlikely

to be explained by genetic factors as no difference in the pattern of anorexia nervosa and autism spectrum disorder among the relatives of female and male index individuals exists[289].

Anorexia nervosa and the autism spectrum share symptoms but their familial coaggregation is nonspecific. The overlap may be influenced by diagnostic insecurities.

1.6 Biology

1.6.1 Sex hormones and disordered eating

Sex hormones have been implicated in the regulation of eating behaviour in several species including humans[293–295]. The effects of sex hormones on the human body are divided in two types: sex hormones have organisational effects during sensitive developmental periods in which they elicit permanent biological alterations within the organism while they also can have transient activational effects that act immediate like the change of eating behaviour during the menstrual cycle[37].

Different approaches were taken to investigate sex hormones in eating disorders. A potential protective effect of prenatal testosterone exposure on female co-twins of male twins in dizygotic twin pairs was postulated, but could not be confirmed in a large study[296], rendering prenatal programming via sex hormones unlikely in anorexia nervosa. Nonetheless, puberty seems to be a clear risk factor for the onset of anorexia nervosa whose period ranges from 13 to 19 years and the higher incidence in females than in males highlights the potential involvement of sex hormones[52,60], but longitudinal studies assessing hormonal concentrations directly in blood or sputum during sensitive periods (e.g., puberty) and relating them to anorexia nervosa are absent. However, preliminary evidence suggests that progesterone may interact with genetic liability and may increase the occurrence of emotional eating in the postovulation phase of the menstrual cycle[297–299]. However, overall findings are mixed and, as yet, larger and more systematic studies are needed to clarify if associations exist[300].

1.6.2 Immune system and inflammation

The human immune system is implicated in several psychiatric disorders, including psychosis and autism[301,302]. Findings of autoantibodies against appetite-regulating hormones, including α-Melanocyte-stimulating hormone (α-MSH), adrenocorticotropic hormone (ACTH), and luteinising hormone-releasing hormone (LHRH), in patients affected by anorexia nervosa[303,304] in combination with the first genome-wide significant hit in a chromosomal region that previously was associated with autoimmune phenotypes[125] fuelled the investigation of a potential involvement of immunological pathways in anorexia nervosa.

Two large record linkage studies in the United Kingdom[305] and in Finland[305,306] indicate bidirectional relationships between autoimmune disease and anorexia nervosa that are confirmed by larger register studies in Denmark[307] and Sweden[56,305]. However, especially autoimmune diseases that predominantly affect the gastrointestinal system, such as ulcerative colitis, Crohn's disease, and celiac disease, present with similar symptoms as anorexia nervosa, including weight loss, indigestion, and food restriction as it often alleviates pain and gastrointestinal bleeding raising the question if patients were potentially misclassified due to symptom overlap[56,305,308].

Additionally, type 1 diabetes, which must be treated with insulin substitution, can precede anorexia nervosa[56,305,306]. Insulin directly affects appetite regulation in the central nervous system and may lead to anorexia nervosa-like syndromes[309]. The identification of bidirectionality between autoimmune disease and anorexia nervosa suggests a shared underlying liability for both; however, no genetic overlap between any autoimmune disease and anorexia nervosa is detected[125,310].

Apart from autoimmune processes, inflammation through infections triggered by virus or bacteria could contribute to the development of anorexia nervosa. One longitudinal study using Swedish and Danish register data shows that individuals that were treated with more than three antiinfectives are at higher risk to get diagnosed with anorexia nervosa[311]. This relationship may be mediated through several factors, including direct effects of the medication, disturbance of microbiome homeostasis, or the antiinfectives may be proxies for the actual viral or bacterial infection which may mediate an inflammatory effect.

Furthermore, patients with anorexia nervosa show higher concentrations of interleukin 6 and tumour necrosis factor α which are regarded as proinflammatory markers[312–314]. However, interleukin 6 is also an important hormone that regulates human fat depots by mobilising lipids during fasting states. The relationship between inflammation and anorexia nervosa is unclear, but it is unlikely that individuals with anorexia nervosa carry a genetic propensity for inflammation as anorexia nervosa and C-reactive protein show a negative genetic correlation, indicating that individuals predisposed to anorexia nervosa carry genetic variants that make them less likely to have elevated C-reactive protein concentrations[310] which is a proxy for inflammatory processes.

1.7 Outlook

A variety of human traits shows a sex bias including psychiatric disorders[315]. More females are affected by eating disorders[52] and major depressive disorder[316] while males more often suffer from attention deficit hyperactivity disorder[317]. Biological sex, however, has woefully been neglected in research which motivated position papers[318–320] demanding the inclusion of biological sex and self-identified gender in future and ongoing projects.

Biological sex has been ingorned in the research of anorexia nervosa. Three major factors hinder the sampling of male anorexia nervosa cases: (1) the prevalences in males is even lower than in females, (2) male patients with psychiatric disorders are less likely to seek help and participate in research, (3) eating disorder research is grossly underfunded limiting the resources that can be allocated to sample difficult-to-reach subpopulations like men and individuals of colour. On grounds of the unexplained sex bias in anorexia nervosa, I approach the research questions in this thesis using genetically-informed techniques and investigate biological sex as potential contributor to or modulator of the liability for anorexia nervosa.

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2 Meta-analysis of cross-sectional and longitudinal studies of body composition in anorexia nervosa

This chapter, synthesising studies on body composition traits in conjunction with laboratory parameters in anorexia nervosa, is presented as a published paper. It is an exact copy of this publication.

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Supplementary materials for this chapter, as detailed in the text, are attached in **Appendix 2** and in the folder **Chapter 2** on the CD.

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REVIEW

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Body composition in anorexia nervosa: Meta-analysis and meta-regression of cross-sectional and longitudinal studies

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Abstract

Objective: Clinically, anorexia nervosa (AN) presents with altered body composition. We quantified these alterations and evaluated their relationships with metabolites and hormones in patients with AN longitudinally.

Method: In accordance with PRISMA guidelines, we conducted 94 meta-analyses on 62 samples published during 1996–2019, comparing up to 2,319 pretreatment, post-treatment, and weight-recovered female patients with AN with up to 1,879 controls. Primary outcomes were fat mass, fat-free mass, body fat percentage, and their regional distribution. Secondary outcomes were bone mineral density, metabolites, and hormones. Meta-regressions examined relationships among those measures and moderators.

Results: Pretreatment female patients with AN evidenced 50% lower fat mass (mean difference [MD]: −8.80 kg, 95% CI: −9.81, −7.79, $Q = 1.01 \times 10^{-63}$) and 4.98 kg (95% CI: −5.85, −4.12, $Q = 1.99 \times 10^{-28}$) lower fat-free mass, with fat mass preferentially stored in the trunk region during early weight restoration (4.2%, 95% CI: −2.1,

Abbreviations: AN, anorexia nervosa; BIA, bioelectrical impedance analysis; DSM, Diagnostic and Statistical Manual of Mental Disorders; DXA, dual-energy X-ray absorptiometry; MD, mean difference; MRI, magnetic resonance imaging; NOS, Newcastle–Ottawa Scale.

−6.2, $Q = 2.30 \times 10^{-4}$). While the majority of traits returned to levels seen in healthy controls after weight restoration, fat-free mass (MD: −1.27 kg, 95% CI: −1.79, −0.75, $Q = 5.49 \times 10^{-6}$) and bone mineral density (MD: −0.10 kg, 95% CI: −0.18, −0.03, $Q = 0.01$) remained significantly altered.

Discussion: Body composition is markedly altered in AN, warranting research into these phenotypes as clinical risk or relapse predictors. Notably, the long-term altered levels of fat-free mass and bone mineral density suggest that these parameters should be investigated as potential AN trait markers.

Resumen

Objetivo: Clínicamente, la anorexia nervosa (AN) se presenta con alteraciones en la composición corporal. Cuantificamos estas alteraciones y evaluamos longitudinalmente su relación con metabolitos y hormonas en pacientes con AN.

Método: De acuerdo con las pautas PRISMA, realizamos 94 meta-análisis en 62 muestras publicadas entre 1996–2019, comparando hasta 2,319 pacientes mujeres en pre-tratamiento, post-tratamiento, y recuperadas en base al peso con hasta 1,879 controles. Las principales medidas fueron masa grasa, masa libre de grasa, porcentaje de grasa corporal y su distribución regional. Las medidas secundarias fueron densidad mineral ósea, metabolitos y hormonas. Las meta-regresiones examinaron las relaciones entre esas medidas y moderadores.

Resultados: Las pacientes femeninas con AN pre-tratamiento mostraron un 50% menos de masa grasa (MD: −8.80 kg, CI 95%: −9.81, −7.79, $Q = 1.01 \times 10^{-63}$) y 4.98 kg (CI 95%: −5.85, −4.12, $Q = 1.99 \times 10^{-28}$) menos de masa libre de grasa, con masa grasa preferentemente almacenada en la región del tronco durante la recuperación temprana del peso (4.2%, CI 95%: −2.1, −6.2, $Q = 2.30 \times 10^{-4}$). Aunque la mayoría de los rasgos regresaron a los niveles vistos en los controles sanos después de la restauración del peso, la masa libre de grasa (MD: −1.27 kg, CI 95%: −1.79, −0.75, $Q = 5.49 \times 10^{-6}$) y la densidad mineral ósea (MD: −0.10 kg, CI 95%: −0.18, −0.03, $Q = 0.01$) permanecieron significativamente alteradas.

Discusión: La composición corporal es marcadamente alterada en la AN, lo que garantiza la investigación en estos fenotipos como predictores de riesgo clínico o de recaída. Notablemente, la alteración a largo plazo de los niveles de masa libre de grasa y densidad mineral ósea sugieren que estos parámetros debe ser investigados como potenciales rasgos indicadores de AN.

KEYWORDS

BIA, binge-eating/purging, bioelectrical impedance analysis, body fat percentage, bone, dual-energy X-ray absorptiometry, DXA, estradiol, fat-free mass, insulin, lean mass, long-term follow-up, restricting, thyroid, weight restoration

1 | INTRODUCTION

Anorexia nervosa (AN) has one of the highest mortality rates of all psychiatric disorders (Chesney, Goodwin, & Fazel, 2014). Clinical observations show altered body composition (El Ghoch, Calugi, Lamburghini, & Dalle Grave, 2014; Solmi et al., 2016) accompanied by elevated cholesterol (Hussain et al., 2019) and greater insulin sensitivity (Ilyas et al., 2018). However, conclusions are limited by small sample sizes and consequent mixed findings.

Molecular genetic studies have revealed that individuals with AN carry genetic variants that increase their liability to AN and concurrently predispose them to lower body fat percentage, lower fasting

insulin, and higher high-density lipoprotein cholesterol concentrations, suggesting that metabolic factors may play an etiological role (Duncan et al., 2017; Watson et al., 2019). Additionally, longitudinal investigations of a British birth cohort showed that girls who develop AN later in life are already underweight at the age of 4 years when compared to healthy children (Yilmaz, Gottfredson, Zerwas, Bulik, & Micali, 2019), adding evidence for a developmental component.

A systematic review showed that adolescents and adults differently lose fat tissue when affected by AN, with adolescents losing more central fat tissue and adults more peripheral fat tissue. During weight recovery, individuals with AN show emergent central adiposity which typically attenuates over time (El Ghoch, Calugi, et al., 2014). These clinical and genetic findings encourage the meta-analytic reassessment of the role of body composition traits, such as fat mass and fat-free mass, their regional distribution, and their changes associated with weight restoration and long-term weight recovery in AN.

Meta-analyses have four major advantages compared to systematic reviews. Increasing statistical power through pooling results from independent samples leads to more precise estimates of the underlying effect. Meta-analyses estimate the heterogeneity (i.e., inconsistency) among effect sizes from the individual studies included, which are crucial for the interpretation of the pooled estimates. Meta-regressions are used to investigate potential moderators of the pooled effect sizes and the relationships between the outcomes of interest, while extensions of meta-analytical models can estimate potential publication bias (Nakagawa, Noble, Senior, & Lagisz, 2017).

The goals of these meta-analyses were to (a) replicate findings from the systematic review on fat mass; (b) extend the observations by quantifying them; (c) include fat-free mass; (d) include bone mineral content and density; (e) investigate their associations with each other; and (f) if possible, relate findings to secondary outcomes, such as metabolic and hormonal parameters. This analytical approach is aimed at understanding the potential associations between these factors that are known to be physiologically interrelated. A thorough and rigorous examination of body composition and related laboratory parameters in individuals with AN could elucidate some of the physiological changes associated with this serious disorder, which could lead to more effective medical management, monitoring, and treatment approaches.

2 | METHOD

2.1 | Search strategy, selection criteria, and data extraction

Our meta-analysis was conducted according to PRISMA guidelines (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009) and preregistered (PROSPERO 2018 CRD42018105338) with no changes to the protocol. We conducted a literature search from June 15, 2018, until July 15, 2019, using the electronic databases PubMed and Web of Science with a time limitation starting with articles published after January 1, 1994—marking the introduction of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV; American Psychiatric Association, 2013). We used key search terms including "anorexia nervosa" AND ("body composition" OR "body fat" OR "fat mass" OR "body fat percentage" OR DXA OR BIA OR "fat free mass" OR "lean mass"). The search was repeated by coauthors to avoid selection bias. Furthermore, we screened the references of published articles and reviews. Our search results, including the selection process, are presented in Figure 1 according to PRISMA guidelines. Our selection criteria are presented in Table 1. In case of multiple publications deriving from the same study population, we selected the articles reporting either the largest or the most recent data set. In case of conflict between these two criteria, large sample size was prioritized. We extracted the information presented in Table 1 from every identified study using a standardized data extraction sheet.

The data extraction sheet was based on two previous meta-analyses (Hussain et al., 2019; Ilyas et al., 2018) and included variables that were hypothesized to be associated with body composition, hormonal, or metabolic measures, including fasting status and period, medications, stage of the menstrual cycle, or treatments for longitudinal studies. If enough studies reported these variables, we performed meta-regressions to investigate their associations with our primary and secondary outcomes.

2.2 | Quality of study assessment (Newcastle–Ottawa scale)

We used the Newcastle–Ottawa Scale (NOS) to assess the quality of nonrandomized studies (Wells et al., 2009). Each study is judged on three broad perspectives: (a) the selection of the study groups; (b) the comparability of the groups; and (c) the ascertainment of the outcome of interest for case–control studies. The NOS evaluates these three quality parameters divided across eight specific items. Each item on the scale is scored from one point, except for comparability, which can be adapted to the specific topic of interest to score up to two points. It has been designed to be used in meta-analyses and systematic reviews. For the observational studies, low quality was defined as NOS score ≤8.0 and high quality as score >8.0 (maximum score 9).

2.3 | Meta-analysis

Inverse variance-weighted meta-analyses for females and males separately were conducted using the statistical package "meta" and "metafor" in the open-source software R v3.5.1 (r-project.org). We used additional formulas to calculate missing values (Hozo, Djulbegovic, & Hozo, 2005; Luo, Wan, Liu, & Tong, 2018; Wan, Wang, Liu, & Tong, 2014). As effect sizes, we estimated mean differences (MDs) between individuals with AN and controls. We chose a random-effects model, which assumes that the heterogeneity in the differences between clinical and control groups is due to both within-study and between-study variation, as we anticipated differences in procedures and study populations between studies. We quantified the heterogeneity through a restricted maximum-likelihood (REML) approach. For the analysis of subtypes, posttreatment, and weight-recovered patients with AN, the control groups from the acutely-ill/pretreatment analysis were reused because (a) control groups were not measured repeatedly and (b) none of the studies had separate control groups for each subtype

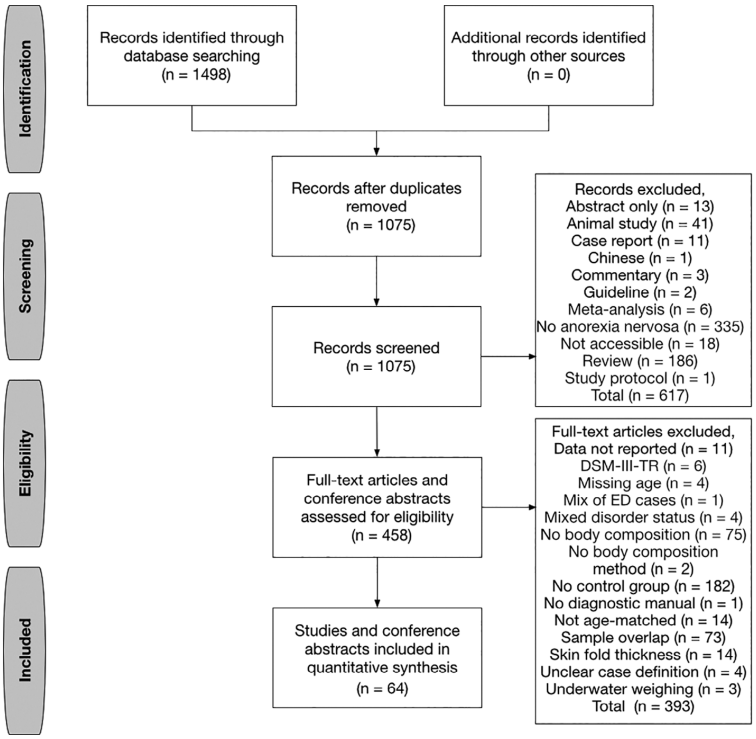

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of study selection

analysis. Although some studies included covariates in their statistical analysis (Bratland-Sanda et al., 2010; Bredella et al., 2008; Dellava, Policastro, & Hoffman, 2009; DiVasta et al., 2007; Fernández-Soto, González-Jiménez, Chamorro-Fernández, & Leyva-Martínez, 2013; Haas et al., 2005; Karlsson, Weigall, Duan, & Seeman, 2000; Kosmiski, Schmiege, Mascolo, Gaudiani, & Mehler, 2014; Maïmoun et al., 2018; Nakahara et al., 2007; Schneider et al., 1998), we only used raw values without including study-specific covariates to increase comparability across individual studies. Weight recovery was defined in accordance with DSM-IV and DSM-5 criteria with BMI >18.5 kg/m^2 or >90% ideal body weight. To correct our primary analysis for multiple testing, false discovery rate–adjusted *Q values* were calculated (Benjamini & Hochberg, 1995).

2.4 | Detection and adjustment for publication bias

The results of meta-analyses can be influenced by publication bias (i.e., small study effects). This describes the phenomenon when certain studies have been selected for publication, while others—mostly due to negative findings—have not been published (Nieminen, Rucker, Miettunen, Carpenter, & Schumacher, 2007). Through graphical diagnosis of asymmetry in funnel plots (Egger, Smith, Schneider, & Minder, 1997) and performing Thompson and Sharp tests (i.e., weighted linear regressions) that take variation between studies into account (Thompson & Sharp, 1999), we investigated potential small study effects or publication bias. If the test resulted in a *p* value below .05, we adjusted the pooled effect estimates using a Copas selection model calculated with the R package "metasens." The model has two components: the first component estimates the pooled effect, while the second estimates a publication probability for each study. A large correlation between these two components suggests that studies with more extreme effects were more likely to be published (Copas, 1999; Copas & Shi, 2000, 2001). The models were iteratively optimized using two tuning parameters γ_0 and γ_1. We present four diagnostic graphics including (a) a funnel plot, (b) a contour plot, (c) a treatment effect plot, and (d) a *p* value plot.

2.5 | Investigation of potential moderators through meta-regression and stratification

To examine the large between-study heterogeneity per meta-analysis (Table 1), we performed meta-regressions using mixed effects models included in the R package "meta" that take the heterogeneity within and between individual studies into account. The models were optimized via a REML approach. Through meta-regression, we investigated whether relevant participant or study characteristics may be associated with the pooled estimates, such as mean age, the time period of follow-up for longitudinal studies, age at diagnosis, age at menarche, age at amenorrhea, duration of illness, percentage of amenorrhea in patients with AN, percentage of medicated patients with AN, percentage of individuals taking

TABLE 1 Selection criteria and extracted data from the original publications

Selection criteria

a. Studies investigating humans only
b. Any age group
c. No sample overlap
d. Observational cross-sectional or longitudinal studies or randomized-controlled trials
e. Clinical diagnoses of AN according to the DSM IV–5, or their revisions (American Psychiatric Association, 2013), or ICD-10 (World Health Organization, 1992)
f. Investigation of body composition by dual-energy X-ray absorptiometry (Bredella et al., 2010, 2013), bioelectrical impedance analysis (BIA) (Bonaccorsi et al., 2012; Mattar et al., 2011), dual photon absorptiometry, or magnetic resonance imaging (Mayer et al., 2005).
g. Published or collected after January 1, 1994 (the year that DSM-IV was introduced)
h. The study includes a control group or comparison group
i. Publications in any language which could be translated by the research team: English, German, Swedish, Danish, Spanish

Extracted data

a. Author, publication year
b. Country
c. Sample sizes including gender and age
d. Setting: Inpatient or outpatient
e. Original longitudinal or cross-sectional design
f. Follow-up period if longitudinal
g. Diagnostic criteria: DSM-IV, DSM-IV-TR, DSM-5, or ICD-10
h. Participant screening and exclusion criteria
i. Number of cases: AN pretreatment, posttreatment (ANpost), recovered from AN (ANrec)
j. Subtype of AN: Restricting (R), binge eating/purging
k. Number of controls
l. Primary outcome variables of body composition: Fat mass, fat-free mass, body fat percentage, and their regional distribution
m. Secondary outcome variables, which were reported by at least three studies additional to primary outcomes: Bone mineral density, glucose, insulin, ghrelin, adiponectin, leptin, insulin-like growth factor, estradiol, testosterone, cortisol, thyroid-stimulating hormone, free triiodothyronine, free thyroxine
n. Covariates used in original analysis
o. Fasting and fasting duration
p. Blood sample: Serum, plasma, or unspecified
q. Medication and contraceptives
r. Psychological and additional treatments
s. Outcome was a secondary or primary outcome in the original study
t. Duration of illness
u. Age at diagnosis/onset
v. Age at menarche
w. Percentage of AN cases with amenorrhea and duration of amenorrhea

Abbreviations: AN, anorexia nervosa; ICD-10, International Classification of Diseases version 10; DSM, Diagnostic and Statistical Manual of Mental Disorders.

contraceptives, body composition measurement method, blood sample type, body composition parameters, and their differences between cases and controls.

A second approach to test for potential moderators is stratification of the sample into meaningful subgroups and estimation of statistical differences between the pooled estimates per subgroup. We used this approach and stratified by AN subtype.

3 | RESULTS

3.1 | Results of the search and selection of studies

A total of 1,498 papers published between 1996 and 2019 were identified by our search terms, and 1,434 (96%) of them were excluded. No paper published during 1994–1996 fulfilled the inclusion criteria, and the most common reasons for exclusion apart from not investigating AN or being a review were (a) no control group (n = 182, 12%); (b) no main outcome reported (i.e., body composition; n = 75, 5%); and (c) sample overlap (n = 73, 5%). Detailed exclusion process is presented in Figure 1. Sixty-four published articles (4%) were included in our analysis, and we became aware of no additional unpublished samples after contacting study authors for additional or missing data (Table S1). The majority of studies focused on female cases and controls that were sampled consecutively in only 22 of 62 samples (35%, Table S2) and aged between 13.8 and 31.3 years (Figure S1). As such, four studies (6%) investigating male AN cases were investigated in a separate quantitative synthesis and are discussed briefly (El Ghoch, Calugi, Milanese, Bazzani, & Dalle Grave, 2017; Marra et al., 2019; Misra et al., 2013; Schorr et al., 2019). Three studies (5%) originated from Australasia, 38 (61%) from Europe, 15 (24%) from North America, and 6 (10%) from Asia. Only 13 studies (21%) used the same method of ascertainment for cases and controls (Table S2). Twenty-nine studies (47%) investigated inpatients, 8 (13%) outpatients, 2 (3%) a mixture of both, and 23 studies (37%) did not specify the recruitment or patient-setting. Twenty-seven studies (44%) comprised collection of blood samples after a fasting period, whereas only six studies (10%) specified the fasting period (Bredella et al., 2012; DiVasta et al., 2011; Dostálová, Sedlácková, Papezová, Nedvídková, & Haluzík, 2009; Estour et al., 2017; Kaválková et al., 2012; Prioletta et al., 2011). One study (3%) did not specify whether analyses were performed using plasma or serum blood (Weinbrenner et al., 2004). Seventeen studies (27%) sampled regular menstruating participants during the follicular phase of their cycle (de Alvaro et al., 2007; Dostálová et al., 2009; Estour et al., 2017; Galusca et al., 2015; Germain et al., 2010, 2007, 2016; Grinspoon et al., 2001; Kaválková et al., 2012; Kirchengast & Huber, 2004; Mayer et al., 2005, 2009; Nakai, Hamagaki, Takagi, Taniguchi, & Kurimoto, 1999; Prioletta et al., 2011; Scalfi et. al, 2002; Weinbrenner et al., 2004), whereas 14 studies (23%) did not provide details about the cycle phase (Bachmann et al., 2014; Bredella et al., 2012; Delporte, Brichard, Hermans, Beguin, & Lambert, 2003; DiVasta et al., 2011; Fazeli et al., 2010; Fernández-Soto et al., 2013; Germain et al., 2010; Gniuli, Liverani, Capristo, Greco, & Mingrone, 2001; Grinspoon et al., 1996; Guo, Jiang, Liao, Liu, & He, 2013; Haas et al., 2005; Karczewska-Kupczewska et al., 2010; Maïmoun et al., 2018; Mörkl et al., 2017; Nakahara et al., 2007; Rigaud, Boulier, Tallonneau, Brindisi, & Rozen, 2010; Tagami et al., 2004; Tanaka et al., 2003). However, studies were retained to achieve the largest possible sample size, and––depending on data availability––meta-regressions were fitted to investigate study characteristics as possible moderators. Originally, 41 studies (66%) were cross-sectional and 21 were longitudinal (34%, Table S1). However, four of the longitudinal studies (19%) were analyzed cross-sectional in our

meta-analysis due to missing data. No control group was repeatedly measured in any of the longitudinal studies.

3.2 | Characteristics of the included studies

We performed four sets of meta-analyses (a) comparing 2,319 pretreatment/acutely ill AN patients with 1,879 healthy controls; (b) comparing 722 post-treatment AN patients with 809 controls; (c) estimating the change in AN patients (n = 722) from pretreatment to posttreatment; and (d) comparing 398 weight-recovered individuals with AN with 660 healthy controls including samples with a long-term follow-up. The pretreatment AN group comprised 229 individuals suffering from the binge-eating/purging (8% of cases) and 701 from the restricting subtype (26% of cases). The shortest follow-up period was 5.14 weeks, and the longest was 2 years (Table S1). Twenty studies (32%) used bioelectrical impedance analysis (BIA) to assess body composition, 39 (63%) used dual-energy X-ray absorptiometry (DXA), and only 3 (5%) utilized magnetic resonance imaging (MRI)––considered to be the benchmark. Thirty of the 62 studies (48%) investigated body composition as a primary outcome, whereas it was a secondary outcome in the remaining studies. The percentage of AN patients with amenorrhea ranged from 0 to 100%, with 11 studies (18%) not providing information on menstrual status (Agüera et al., 2015; Bachmann et al., 2014; Bredella et al., 2012; de Mateo Silleras et al., 2013; El Ghoch et al., 2012; Gniuli et al., 2001; Iacopino et al., 2003; Kirchengast & Huber, 2004; Schneider et al., 1998; Tagami et al., 2004; Tanaka et al., 2003). Thirty-five of 62 studies (56%) did not provide information on the medication status of AN patients, and 32 (52%) did not indicate whether oral contraceptives were used. In AN cases, the duration of illness was on average 52.2 months (SD = 29.4), the duration of amenorrhea 23.0 months (SD = 18.3), and the age at diagnosis 17.5 years (SD = 3.0). Cases and controls were well matched for age (Figure S1) and, notably, we did not observe a difference in age at menarche (Figure S2) or height (Figure S5) between AN cases and controls.

3.3 | Data and analyses results of meta-analyses and meta-regressions

Our results from the 94 meta-analyses show that a wide range of alterations in several key body composition and biochemical measures exist in AN cases compared with healthy controls (Figure 2 and Figure S3). For 95% confidence intervals and Q values, heterogeneity estimates (τ^2 and I^2), and adjusted estimates due to estimated publication bias, see Table 2. Detailed forest plots showing each of the 94 meta-analyses are presented as Figures S4–S89 for females and Figures S90–S95 for males. No differences between restricting and binge-eating/purging subtype of AN were detected in our meta-analysis prior to treatment except for total body water (Table S3). Between-study heterogeneity (I^2) was observed in 62 meta-analyses (70%) and ranged from 52 to 99%, confirming our choice of a random-effects model. To investigate moderators implicated in heterogeneity, we performed 411 meta-regressions (Tables S4–S7). Six meta-analyses showed funnel plot asymmetry, indicating small study effects. Therefore, we fitted Copas models to adjust for those effects and estimate the probable number of unpublished studies (Table 1 and Figures S96–S101).

3.4 | Primary outcomes: Body composition

3.4.1 | Anthropometrics

On average, pretreatment female AN cases had a 15.64 kg (95% CI: −16.98, −14.30, $Q = 5.59 \times 10^{-114}$) lower body weight and were 0.01 m (95% CI: −0.02, 0.00, Q = 0.02) shorter than healthy controls (Table S4). After treatment, female AN patients still weighed 4.92 kg (95% CI: −8.03, −1.81, $Q = 1.92 \times 10^{-3}$) less than healthy controls. Before treatment, male AN cases weighed 15.48 kg (95% CI: −22.42, −8.54, $Q = 1.80 \times 10^{-5}$) less than healthy controls and showed no differences in height compared with controls.

Correspondingly, the pretreatment BMI difference between female AN cases and controls was −5.81 kg/m^2 (95% CI: −6.25, −5.38, $Q = 2.83 \times 10^{-152}$), which reduced to −2.10 kg/m^2 (95% CI: −2.53, −1.67, $p_{adjCopas} < .0001$) after treatment as most patients gained on average 9.93 kg (95% CI: 8.17, 11.68, $Q = 2.11 \times 10^{-27}$) during treatment. Posttreatment BMI in females was primarily accounted for by gains in fat mass ($\beta_{metareg}$ = 0.81, $p = 7.03 \times 10^{-7}$) but not through fat-free mass (Table S5). After weight recovery, no statistically significant MD in BMI between female AN cases and controls was detected. The pretreatment BMI difference between male AN cases and controls was −5.48 kg/m^2 (95% CI: −7.87, −3.09, $Q = 1.80 \times 10^{-5}$).

3.4.2 | Fat mass

The pretreatment body composition of individuals with AN was significantly altered. Compared with healthy controls, female AN cases had 8.80 kg (95% CI: −9.81, −7.79, $Q = 1.01 \times 10^{-63}$) lower fat mass, corresponding to a 13.9% (95% CI: −15.1, −12.6, $Q = 5.49 \times 10^{-101}$; Figure 3) lower total body mass. Male AN cases had 5.87 kg (95% CI: −8.98, −2.75, $Q = 2.70 \times 10^{-4}$) lower fat mass, corresponding to 7.5% (95% CI: −10.8, −4.2, $Q = 1.8 \times 10^{-5}$) lower total body mass. This suggests that body fat was on average 50% lower than in healthy controls. Body fat percentage ($\beta_{metareg}$ = −134.53, p = 0.01) and absolute fat mass ($\beta_{metareg}$ = −35.50, $p = 2.03 \times 10^{-5}$) were associated with whole-body bone mineral density of female AN patients. Absolute fat mass was also associated with mean age at diagnosis ($\beta_{metareg}$ = −1.21, $p = 2.42 \times 10^{-4}$) in females (Table S4).

After treatment, female AN patients had a 2.37 kg (95% CI: −3.75, −0.98, Q = 0.002) lower fat mass, which corresponded to 2.5% (95% CI: −4.3, −0.7, $p_{adjCopas}$ = 0.006) less total body mass compared with healthy controls. Female AN patients gained 6.39 kg (95% CI: 5.13, 7.65, $Q = 3.07 \times 10^{-22}$) fat mass following treatment, which corresponded to 10.4% (95% CI: 7.96, 12.87, $Q = 6.25 \times 10^{-16}$) of total body mass. Posttreatment fat mass ($\beta_{metareg}$ = −0.23, p = .01; Table S5) and gain in fat mass during treatment ($\beta_{metareg}$ = −0.20,

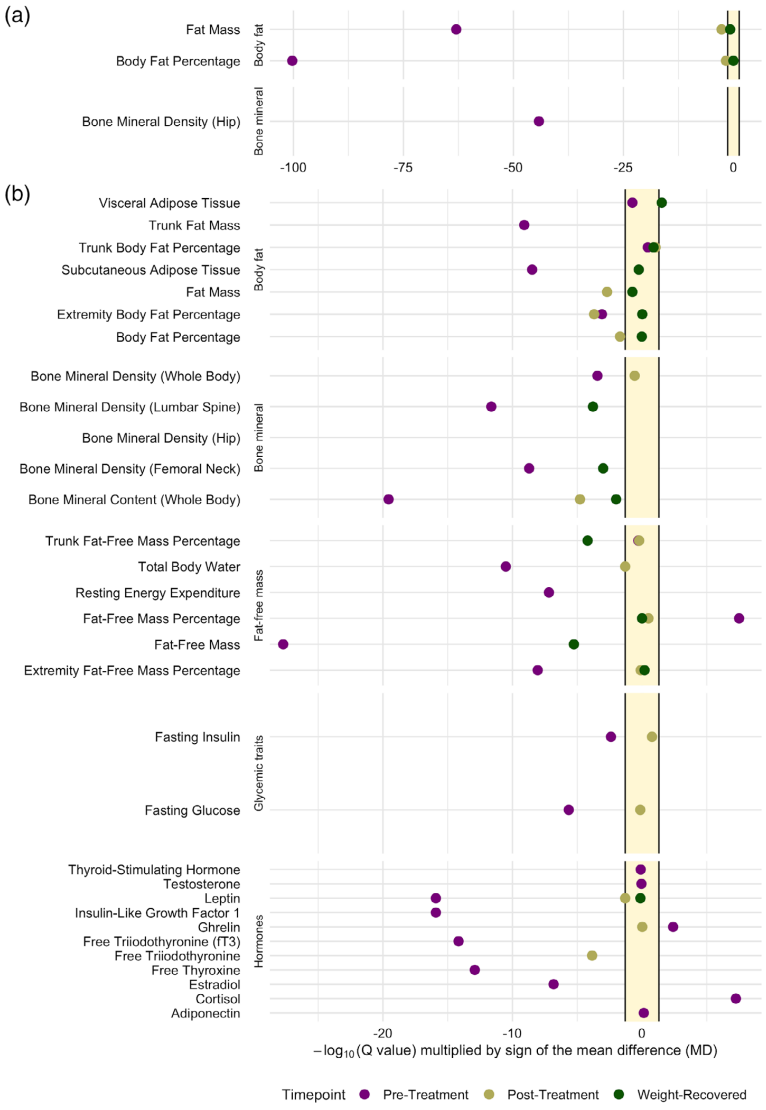

FIGURE 2 Summary plot of all 88 meta-analyses comparing female AN cases with healthy controls. The plot shows the *Q* values (i.e., the false discovery rate-corrected *p* values) of each inverse variance-weighted random-effects meta-analyses comparing AN cases pretreatment (purple, *n* = up to 2,294), posttreatment (light green, *n* = up to 722), and after weight recovery (dark green, *n* = up to 398) with healthy controls (*n* = up to 2,251). Restricted maximum-likelihood estimator was used to estimate heterogeneity. *Q* values are transformed on the -$\log_{10}$ scale, multiplied by the sign of the mean difference (MD) and presented on the *x*-axis. Points lying in the yellow area indicate no statistically significant mean difference between AN cases and healthy controls after correction for multiple testing (i.e., $Q > 0.05$). Points to the left of the yellow area indicate a lower mean value in AN cases than in controls, whereas points on the right of the yellow area indicate a higher mean value in AN cases than in controls. A dark green point outside the yellow area indicates a significant difference between AN cases and controls after weight recovery (a) The outcomes with the largest differences between cases and controls. (b) The less extreme mean differences. The *x*-axis was capped at -$\log_{10}$(*Q* value) × sign(MD) = −0.25. The full figure is presented as Figure S3 [Color figure can be viewed at wileyonlinelibrary.com]

p = .02; Table S6) were negatively associated with the presence of amenorrhea. Following weight recovery, these values fully returned to levels seen in female healthy controls.

Specifically, compared with healthy controls, female AN patients had 3.51 kg (95% CI: −4.58, −2.43, $Q = 8.07 \times 10^{-10}$) less trunk fat mass prior to treatment. In relative terms, however, female AN patients had lower extremity body fat with 5.4% (95% CI: −8.4, −2.4, $Q = 8.23 \times 10^{-4}$) less total body mass. The presence of amenorrhea was significantly associated with lower extremity fat mass ($\beta_{metareg} = 0.31$, $p = .04$; Table S4).

After treatment, female AN patients showed a higher trunk body fat percentage than controls at 12.0% (95% CI: 9.5, 14.4, $p_{adjCopas} < 1.00 \times 10^{-4}$) of total body mass. However, this finding was strongly influenced by publication bias with an estimated 52 unpublished studies. These results on body composition were not influenced by height as female and male cases and controls showed no meaningful difference (i.e., 1 cm pretreatment) or by age as meta-regressions were nonsignificant (Tables S4–S7).

3.4.3 | Fat-free mass

Overall, the fat-free mass in female AN patients was 4.98 kg (95% CI: −5.85, −4.12, $Q = 1.99 \times 10^{-28}$; Figure 4) lower before treatment than in controls, corresponding to 12.3% (95% CI: 8.1, 16.5,

TABLE 2 Overview table over all 94 fitted inverse-variance weighted random-effects meta-analyses comparing female or male anorexia nervosa (AN) patients and healthy controls (CO) pretreatment, posttreatment, and after weight recovery and additional meta-analyses estimating the change in female AN patients before and after treatment

Female		Number of participants				Meta-analysis					Heterogeneity				Small study effects					
Pretreatment outcome	*k*	AN	CO	Min	Max	MD	Unit	95% CI	*p*	Q	τ^2	I^2	95% CI	*p*	T&S	Copas	95% CI	*p*	*N* unpub	Reference values
Weight	36	1,444	1,536	−26.60	−4.00	−15.64	kg	−16.98, −14.30	1.27×10^{-115}	5.59×10^{-114}	13.41	84.6%	79.6%, 88.4%	4.12×10^{-30}	0.76					
Height	26	1,499	1,255	−0.05	0.03	−0.01	m	−0.02, 0.00	.01	0.02	0.0001	66.7%	49.7%, 77.9%	6.86×10^{-7}	0.12					
Body mass index	56	2,742	2,302	−9.90	−2.10	−5.81	kg/m^2	−6.25, −5.38	3.22×10^{-154}	2.83×10^{-152}	2.43	93.4%	92.2%, 94.5%	2.27×10^{-140}	0.10					18.5–24.9 kg/m^2
Fat mass	40	2,193	1,720	−20.50	−1.54	−8.80	kg	−9.81, −7.79	4.58×10^{-65}	1.01×10^{-63}	9.64	96.0%	95.3%, 96.7%	2.97×10^{-181}	0.59					
Body fat percentage	44	2,179	1803	−24.60	−5.50	−13.84	%	−15.10, −12.58	1.87×10^{-102}	5.49×10^{-101}	15.84	92.8%	91.2%, 94.1%	1.40×10^{-98}	0.31					20%–25%
Visceral adipose tissue	2	44	115	−1.02	−0.21	−0.62	kg	−1.41, 0.18	.13	0.18	0.32	99.0%	97.9%, 99.5%	1.67×10^{-22}						
Subcutaneous adipose tissue	2	44	115	−10.71	−7.70	−9.26	kg	−12.21, −6.31	7.46×10^{-10}	3.28×10^{-9}	4.24	93.5%	78.9%, 98.0%	8.63×10^{-5}						
Trunk fat mass	4	72	88	−4.50	−2.40	−3.51	kg	−4.58, −2.43	1.65×10^{-10}	8.07×10^{-10}	0.88	73.8%	26.7%, 90.7%	.009	0.83					
Trunk body fat percentage	7	199	245	−5.65	6.40	1.77	%	−1.46, 5.01	.28	0.36	16.72	91.1%	84.2%, 95.0%	1.36×10^{-12}	0.96					
Extremity body fat percentage	5	129	124	−9.00	0.53	−5.40	%	−8.38, −2.43	3.74×10^{-4}	8.03×10^{-4}	8.47	71.5%	27.8%, 88.7%	7.25×10^{-3}	0.37					
Fat-free mass	37	2,319	1879	−12.16	0.20	−4.98	kg	−5.85, −4.12	1.36×10^{-29}	1.99×10^{-28}	5.92	90.5%	87.9%, 92.5%	1.22×10^{-58}	0.51					
Fat-free mass percentage	9	562	528	−0.10	20.47	12.29	%	8.12, 16.47	8.03×10^{-9}	3.21×10^{-8}	39.60	99.6%	99.6%, 99.7%	.00	0.21					
Trunk fat-free mass percentage	3	124	133	−2.41	0.20	−0.19	%	−0.66, 0.27	.42	0.52	0.00	55.8%	0.0%, 87.4%	.10						
Extremity fat-free mass percentage	3	124	133	−1.84	−1.00	−1.53	%	−2.03, −1.03	2.11×10^{-9}	8.84×10^{-9}	0.00	0.0%	0.0%, 81.7%	.57						
Bone mineral content (whole body)	6	585	358	−0.70	−0.11	−0.16	kg	−0.19, −0.12	3.10×10^{-21}	2.73×10^{-20}	0.00	58.2%	0.0%, 83.1%	.04	0.08					
Bone mineral density (whole body)	15	1,000	593	−0.41	0.04	−0.07	g/cm^2	−0.11, −0.04	1.64×10^{-4}	3.61×10^{-4}	0.005	80.3%	68.3%, 87.7%	1.30×10^{-9}	0.002	−0.03	−0.06, −0.01	0.02	9	
Bone mineral density (lumbar spine)	12	871	682	−0.27	0.01	−0.14	g/cm^2	−0.18, −0.10	4.22×10^{-13}	2.32×10^{-12}	0.004	83.2%	72.0%, 89.9%	9.28×10^{-10}	0.87					
Bone mineral density (femoral neck)	11	1,109	723	−0.28	0.03	−0.14	g/cm^2	−0.18, −0.09	4.16×10^{-10}	1.93×10^{-9}	0.004	85.9%	76.5%, 91.5%	2.98×10^{-11}	0.81					
Bone mineral density (hip)	7	945	406	−0.15	0.03	−0.13	g/cm^2	−0.15, −0.11	3.52×10^{-46}	6.20×10^{-45}	0.0002	52.0%	0.0%, 79.6%	.05	0.22					
Total body water	6	342	254	−6.82	−2.60	−4.77	L	−6.13, −3.41	5.92×10^{-12}	3.06×10^{-11}	1.95	78.3%	52.1%, 90.1%	3.36×10^{-4}	0.72					3.3–3.6 L
Resting energy expenditure	3	99	128	−536.00	−296.37	−393.95	kcal/day	−531.04, −256.86	1.78×10^{-8}	6.53×10^{-8}	12,736.55	85.9%	59.0%, 95.2%	8.30×10^{-4}						
Fasting glucose	7	111	107	−26.49	−7.21	−11.44	mg/dl	−15.95, −6.93	6.71×10^{-7}	2.21×10^{-6}	28.76	73.9%	44.2%, 87.8%	8.04×10^{-4}	0.03	−7.01	−9.61, −4.40	<0.0001	11	<140 mg/dl
Fasting insulin	9	222	221	−42.01	7.83	−19.23	pmol/L	−31.68, −6.77	.002	0.004	282.08	91.2%	85.5%, 94.6%	3.43×10^{-16}	0.40					<173.6 pmol/L
Ghrelin	4	123	83	15.00	217.50	149.20	pmol/L	54.59, 243.81	.002	0.004	7,872.55	88.3%	72.4%, 95.0%	1.19×10^{-5}	0.61					114.4–154 pmol/L
Adiponectin	4	104	88	−7.30	7.28	1.37	μg/ml	−4.36, 7.11	.64	0.73	30.55	86.6%	67.4%, 94.4%	5.62×10^{-5}	0.52					4–37 μg/ml
Leptin	19	771	544	−14.10	−0.46	−7.90	ng/ml	−9.72, −6.08	1.55×10^{-17}	1.22×10^{-16}	14.25	94.1%	92.0%, 95.6%	6.47×10^{-54}	0.04	−7.20	−8.44, −5.96	<0.0001	5	3.3–18.3 ng/ml
Testosterone	4	99	98	−18.23	18.30	−1.35	ng/dl	−16.03, 13.33	.86	0.90	144.92	69.4%	11.9%, 89.4%	.02	0.91					23–75 ng/dl
Thyroid-stimulating hormone	5	188	196	−0.80	0.30	−0.06	μIU/ml	−0.40, 0.27	.72	0.79	0.08	55.5%	0.0%, 83.6%	.06	0.30					0.4–4.8 μIU/L

(Continues)

TABLE 2 (Continued)

Female		Number of participants				Meta-analysis					Heterogeneity				Small study effects					
Pretreatment outcome	***k***	**AN**	**CO**	**Min**	**Max**	**MD**	**Unit**	**95% CI**	***p***	**Q**	τ^2	I^2	**95% CI**	***p***	**T&S**	**Copas**	**95% CI**	***p***	***N* unpub**	**Reference values**
Free triiodothyronine	8	251	215	−2.14	−0.73	−1.32	pmol/L	−1.64, −1.00	1.09×10^{-15}	6.85×10^{-15}	0.17	85.7%	73.7%, 92.2%	2.41×10^{-8}	0.14					3.5–9.5 pmol/L
Free thyroxine	4	173	177	−3.40	−2.19	−2.60	pmol/L	−3.26, −1.93	2.09×10^{-14}	1.23×10^{-13}	0.19	36.8%	0.0%, 78.2%	.19	0.88					13–27 pmol/L
Insulin-like growth factor 1	9	233	186	−140.30	−41.00	−95.86	ng/ml	−117.93, −73.8	1.67×10^{-17}	1.22×10^{-16}	747.86	72.2%	45.3%, 85.8%	3.50×10^{-4}	0.91					130–450 ng/ml
Cortisol	7	209	167	50.00	232.00	131.92	nmol/L	86.26, 177.58	1.49×10^{-8}	5.70×10^{-8}	2,649.65	72.6%	40.9%, 87.3%	.001	0.85					170–635 nmol/L (8:00 a.m.)
Estradiol	11	278	231	−72.41	−1.86	−40.83	pg/ml	−55.43, −26.23	4.22×10^{-8}	1.49×10^{-7}	526.46	99.1%	98.9%, 99.3%	9.60×10^{-237}	0.87					20–50 pg/ml
Male		**Number of participants**				**Meta-analysis**					**Heterogeneity**				**Small study effects**					
Pretreatment	***k***	**AN**	**CO**	**Min**	**Max**	**MD**	**Unit**	**95% CI**	***p***	**Q**	τ^2	I^2	**95% CI**	***p***	**T&S**	**Copas**	**95% CI**	***p***	***N* unpub**	**Reference values**
Weight	2	32	34	−18.50	−11.33	−15.48	kg	−22.42, −8.54	1.22×10^{-5}	1.80×10^{-05}	17.94	69.8%	0.0%, 93.2%	.07						
Height	3	42	44	−0.03	0.00	−0.02	m	−0.04, 0.01	.13	0.13	0.00	0.0%	0.0%, 82.7%	.55						
Body mass index	4	68	92	−9.00	−3.70	−5.48	kg/m^2	−7.87, −3.09	6.92×10^{-06}	1.80×10^{-05}	5.58	94.2%	88.2%, 97.1%	3.65×10^{-11}	0.89					18.5–24.9 kg/m^2
Fat mass	3	42	44	−8.70	−3.03	−5.87	kg	−8.98, −2.75	2.22×10^{-04}	2.70×10^{-04}	6.77	87.2%	63.5%, 95.5%	4.17×10^{-04}						
Body fat percentage	4	68	92	−9.70	−2.40	−7.49	%	−10.79, −4.19	8.76×10^{-06}	1.80×10^{-05}	9.84	85.7%	64.8%, 94.2%	1.07×10^{-04}	0.70					12%–14%
Fat-free mass	3	42	44	−10.20	−5.25	−9.37	kg	−12.47, −6.27	3.30×10^{-09}	2.00×10^{-08}	0.00	0.0%	0.0%, 66.3%	.73						
Female		**Number of participants**				**Meta-analysis**					**Heterogeneity**				**Small study effects**					
Posttreatment	***k***	**AN**	**CO**	**Min**	**Max**	**MD**	**Unit**	**95% CI**	***p***	**Q**	τ^2	I^2	**95% CI**	***p***	**T&S**	**Copas**	**95% CI**	***p***	***N* unpub**	**Reference values**
Weight	12	398	492	−16.60	0.60	−4.92	kg	−8.03, −1.81	1.92×10^{-3}	0.004	27.82	92.6%	89%, 95.1%	1.82×10^{-26}	0.15					
Height	2	146	141	−0.01	0.01	0.00	m	−0.02, 0.02	.79	0.84				.22						
Body mass index	18	722	809	−5.50	0.20	−2.35	kg/m^2	−3.28, −1.42	6.79×10^{-7}	2.21×10^{-6}	3.81	97.6%	97.0%, 98.1%	3.96×10^{-138}	0.04	−2.10	−2.53, −1.67	<.0001	5	18.5–24.9 kg/m^2
Fat mass	15	589	617	−6.89	1.70	−2.37	kg	−3.75, −0.98	8.29×10^{-4}	0.002	6.65	94.6%	92.5%, 96.1%	5.45×10^{-47}	0.73					
Body fat percentage	14	530	617	−14.29	2.40	−3.15	%	−5.61, −0.70	.01	0.02	19.77	89.0%	83.3%, 92.7%	5.37×10^{-19}	0.05	−2.50	−4.27, −0.73	.006	3	20%–25%
Trunk body fat percentage	6	179	224	−8.24	12.30	5.84	%	−0.14, 11.83	.06	0.09	53.72	94.4%	90.4%, 96.8%	7.59×10^{-18}	0.03	11.99	9.54, 14.44	<.0001	52	
Extremity body fat percentage	5	129	124	−10.00	0.10	−6.37	%	−9.52, −3.23	7.24×10^{-5}	1.82×10^{-4}	10.48	78.1%	47.5%, 90.9%	.001	0.08					
Fat-free mass	12	634	697	−4.80	0.20	−1.82	kg	−2.57, −1.08	1.72×10^{-6}	5.41×10^{-6}	0.98	60.2%	25.0%, 78.9%	.004	0.61					
Fat-free mass percentage	6	239	299	−1.00	14.29	2.83	%	−1.89, 7.55	.24	0.32	33.35	93.5%	88.5%, 96.3%	3.89×10^{-15}	0.08					
Trunk fat-free mass percentage	3	124	133	−1.09	0.90	−0.40	%	−1.57, 0.77	.50	0.60	0.85	77.9%	28.8%, 93.2%	.01						
Extremity fat-free mass percentage	3	124	133	−1.90	1.20	−0.30	%	−1.97, 1.37	.73	0.79	1.93	85.0%	55.7%, 94.9%	.001						
Bone mineral content (whole body)	2	174	194	−0.09	−0.09	−0.09	kg	−0.13, −0.05	5.75×10^{-6}	1.63×10^{-5}				1.00						
Bone mineral density (whole body)	2	74	67	−0.04	−0.01	−0.02	g/cm^2	−0.04, 0.01	.20	0.27				.34						
Total body water	3	204	159	−6.66	−0.80	−3.71	L	−7.07, −0.36	.03	0.05	8.25	95.1%	88.9%, 97.8%	1.59×10^{-9}						3.3–3.6 L

(Continues)

TABLE 2 (Continued)

Female		Number of participants				Meta-analysis					Heterogeneity				Small study effects					
Posttreatment	*k*	AN	CO	Min	Max	MD	Unit	95% CI	*p*	Q	τ^2	I^2	95% CI	*p*	T&S	Copas	95% CI	*p*	*N* unpub	Reference values
Fasting glucose	3	45	41	−8.83	5.41	−1.78	mg/dl	−8.98, 5.42	.63	0.73	28.75	66.9%	0.0%, 90.5%	.05						<140 mg/dl
Fasting insulin	3	46	74	−4.90	9.72	8.31	pmol/L	−2.26, 18.87	.12	0.17	0	0.0%	0.0%, 64.8%	.74						<173.6 pmol/L
Ghrelin	2	33	61	−89.00	105.00	7.34	pmol/L	−182.77, 197.45	.94	0.96	17,674.47	93.9%	80.6%, 98.1%	4.98×10^{-5}						114.4–154 pmol/L
Leptin	5	72	113	−9.18	−0.40	−3.91	ng/ml	−7.37, −0.45	.03	0.05	12.07	81.3%	56.6%, 92%	2.59×10^{-4}	0.17					3.3–18.3 ng/ml
Free triiodothyronine	2	33	63	−1.00	−0.90	−0.91	pmol/L	−1.36, −0.47	5.26×10^{-5}	1.40×10^{-4}				.88						3.5–9.5 pmol/L
Female		**Number of participants**				**Meta-analysis**					**Heterogeneity**				**Small study effects**					
Pretreatment/ posttreatment	*k*	AN	CO	Min	Max	MD	Unit	95% CI	*p*	Q	τ^2	I^2	95% CI	*p*	T&S	Copas	95% CI	*p*	*N* unpub	Reference values
Weight	12	398	436	4.30	16.00	9.93	kg	8.17, 11.68	1.44×10^{-28}	2.11×10^{-27}	7.54	80.0%	65.0%, 88.0%	1.35×10^{-7}	0.32					
Height	2	146	146	0.00	0.01	0.00	m	−0.01, 0.02	.67	0.75				.53						
Body mass index	18	722	807	1.16	6.40	3.39	kg/m^2	2.71, 4.08	4.19×10^{-22}	4.10×10^{-21}	1.99	95.0%	94.0%, 97.0%	8.54×10^{-68}	0.37					18.5–24.9 kg/m^2
Fat mass	15	589	636	−0.86	8.90	6.39	kg	5.13, 7.65	2.79×10^{-23}	3.07×10^{-22}	5.42	95.0%	93.0%, 96.0%	7.66×10^{-49}	0.68					
Body fat percentage	14	530	530	3.85	15.70	10.41	%	7.96, 12.87	9.23×10^{-17}	6.25×10^{-16}	19.21	93.0%	90.0%, 95.0%	2.07×10^{-32}	0.40					20%–25%
Trunk body fat percentage	6	179	179	−2.59	6.20	4.16	%	2.07, 6.25	9.67×10^{-5}	2.30×10^{-4}	4.08	59.0%	0.0%, 83.0%	3.25×10^{-2}	0.08					
Extremity body fat percentage	5	129	129	−1.10	−0.43	−0.95	%	−2.61, 0.71	.26	0.34	0	0.0%	0.0%, 0.0%	1.00	0.83					
Fat-free mass	12	634	719	0.00	6.90	2.98	kg	1.74, 4.22	2.35×10^{-6}	6.89×10^{-6}	3.87	93.0%	89.0%, 95.0%	4.57×10^{-27}	0.66					
Fat-free mass percentage	6	239	239	−13.92	0.10	−9.00	%	−13.63, −4.37	1.38×10^{-4}	3.11×10^{-4}	31.68	99.0%	99.0%, 99.0%	9.94×10^{-112}	0.49					
Trunk fat-free mass percentage	3	124	124	−0.73	1.32	0.17	%	−1.06, 1.40	.79	0.84	0.78	72.3%	6.5%, 91.8%	.03						
Extremity fat-free mass percentage	3	124	124	−0.90	3.04	1.01	%	−1.08, 3.10	.34	0.43	2.83	84.6%	54.2%, 94.8%	.002						
Bone mineral content (whole body)	2	174	174	0.05	0.07	0.05	kg	0.02, 0.09	.006	0.01				.74						
Bone mineral density (whole body)	2	74	74	−0.01	0.01	0.01	g/cm^2	−0.02, 0.03	.64	0.73				.53						
Total body water	3	204	251	0.16	1.80	0.58	L	−0.24, 1.40	.17	0.23	0.18	30.8%	0.0%, 92.8%	.24						3.3–3.6 L
Fasting glucose	3	45	45	5.23	16.22	9.51	mg/dl	2.68, 16.35	.006	0.01	23.25	66.3%	0.0%, 90.3%	.05						<140 mg/dl
Fasting insulin	3	46	84	9.03	38.19	15.92	pmol/L	1.89, 29.95	.03	0.05	42.79	24.2%	0.0%, 92.1%	.27						<173.6 pmol/L
Ghrelin	2	33	71	−112.50	−104.00	−107.76	pmol/L	−161.47, −54.05	8.41×10^{-5}	2.06×10^{-4}				.88						114.4–154 pmol/L
Leptin	5	72	110	1.10	5.50	2.83	ng/ml	1.22, 4.44	5.79×10^{-4}	0.001	2.41	71.0%	26.0%, 89.0%	.008	0.42					3.3–18.3 ng/ml
Free triiodothyronine	2	33	71	0.80	0.80	0.80	pmol/L	0.39, 1.21	1.33×10^{-4}	3.08×10^{-4}				1.00						3.5–9.5 pmol/L

(Continues)

TABLE 2 (Continued)

Female Weight-recovered	*k*	Number of participants AN	CO	Min	Max	Meta-analysis MD	Unit	95% CI	*p*	*Q*	Heterogeneity τ^2	I^2	95% CI	*p*	Small study effects T&S	Copas	95% CI	*p*	*N* unpub	Reference values
Weight	11	305	530	−8.70	1.65	−1.83	kg	−3.68, 0.02	.05	0.08	5.80	66.4%	36.4%, 82.2%	.001	0.95					
Height	6	174	341	−0.03	−0.01	−0.01	m	−0.03, 0.00	.02	0.03	0.00	0.0%	0.0%, 0.0%	.94	0.51					
Body mass index	12	398	660	−2.80	0.50	−0.68	kg/m^2	−1.38, 0.02	.06	0.09	1.17	93.3%	90.2%, 95.5%	1.16×10^{-29}	0.84					18.5–24.9 kg/m^2
Fat mass	12	323	563	−6.30	1.70	−0.76	kg	−1.75, 0.22	.13	0.18	1.82	63.0%	31.0%, 80.1%	.002	0.47					
Body fat percentage	10	392	463	−2.32	2.40	−0.03	%	−1.09, 1.02	.95	0.96	1.06	39.0%	0.0%, 70.9%	.10	0.44					14%–25%
Visceral adipose tissue	2	37	18	0.10	0.24	0.19	kg	0.03, 0.35	.02	0.03				.42						
Subcutaneous adipose tissue	2	37	18	−0.52	−0.42	−0.50	kg	−1.81, 0.82	.46	0.56				.95						
Trunk body fat percentage	5	147	207	−3.30	12.30	5.86	%	−0.83, 12.54	.09	0.13	55.17	96.3%	93.7%, 97.8%	1.75×10^{-22}	0.28					
Extremity body fat percentage	3	81	89	−10.00	20.09	0.53	%	−18.65, 19.71	.96	0.96	285.64	99.4%	99.1%, 99.6%	7.45×10^{-72}						
Fat-free mass	9	381	645	−2.10	−0.30	−1.27	kg	−1.79, −0.75	1.81×10^{-6}	5.49×10^{-6}	0.03	0.0%	0.0%, 39.7%	.79	0.54					
Fat-free mass percentage	4	206	256	−1.00	0.00	0.00	%	−0.06, 0.06	.95	0.96	0.00	0.0%	0.0%, 70.9%	.66	0.35					
Trunk fat-free mass percentage	2	105	113	−1.11	−0.88	−0.91	%	−1.33, −0.49	2.29×10^{-5}	6.30×10^{-5}				.72						
Extremity fat-free mass percentage	2	105	113	−0.27	1.59	0.56	%	−1.25, 2.37	.54	0.64	1.49	86.2%	45.0%, 96.5%	.01						
Bone mineral content (whole body)	2	134	161	−0.23	−0.09	−0.10	kg	−0.18, −0.03	.008	0.01	0.001	12.9%	NA%, NA%	.28						
Bone mineral density (lumbar spine)	2	31	210	−0.09	−0.04	−0.08	g/cm^2	−0.12, −0.04	6.28×10^{-5}	1.63×10^{-4}				.39						
Bone mineral density (femoral neck)	2	31	210	−0.11	−0.05	−0.10	g/cm^2	−0.15, −0.04	5.31×10^{-4}	0.001				.40						
Leptin	2	13	30	−1.30	−0.40	−0.43	ng/ml	−2.41, 1.55	.67	0.75				.87						3.3–18.3 ng/ml

To correct for multiple comparison, we calculated FDR-adjusted *Q* values. To test for small study effects or publication bias, we performed a Thompson and Sharp (T&S) test. A *p* value below .05 indicated small study effects or publication bias. In this case, a Copas model was fitted to adjust the original meta-analysis (Agüera et al., 2015; Bachmann et al., 2014; Benninghoven, Raykowski, Solzbacher, Kunzendorf, & Jantschek, 2007; Bratland-Sanda et al., 2010; Bredella et al., 2012, 2008; Chudecka & Lubkowska, 2016; de Alvaro et al., 2007; Dellava et al., 2009; Delporte et al., 2003; de Mateo Silleras et al., 2013; Diamanti et al., 2007; DiVasta et al., 2007, 2011; Dostálová et al., 2009; El Ghoch et al., 2012, 2015; El Ghoch, Calugi, et al., 2017; El Ghoch, Milanese, et al., 2014; El Ghoch, Pourhassan, et al., 2017; Estour et al., 2017; Faje et al., 2014; Fazeli et al., 2010; Fernández-Soto et al., 2013; Galusca et al., 2015; Germain et al., 2010, 2007, 2016; Gniuli et al., 2001; Grinspoon et al., 1996, 2001; Guo et al., 2013; Haas et al., 2018, 2005; Iacopino et al., 2003; Karczewska-Kupczewska et al., 2010; Karlsson et al., 2000; Kaválková et al., 2012; Kerruish et al., 2002; Kirchengast & Huber, 2004; Konstantynowicz et al., 2011; Kosmiski et al., 2014; Maïmoun et al., 2018; Marra et al., 2019; Mayer et al., 2009, 2005; Mika, Herpertz-Dahlmann, Heer, & Holtkamp, 2004; Misra et al., 2013; Moreno, Djeddi, & Jaffrin, 2008; Mörkl et al., 2017; Nakahara et al., 2007; Nakai et al., 1999; Prioletta et al., 2011; Rigaud et al., 2010; Scalfi, Marra, Caldara, Silvestri, & Contaldo, 1999; Scalfi et al., 2002; Schneider et al., 1998; Schorr et al., 2019; Singhal et al., 2018; Tagami et al., 2004; Tanaka et al., 2003; Tonhajzerova et al., 2019; Weinbrenner et al., 2004; Wu et al., 2019).

Abbreviations: 95% CI, 95% confidence interval; AN, anorexia nervosa; CO, controls; Copas, Copas model; *k*, number of studies; MD, mean difference; T&S, Thompson & Sharp; *N* unpub, number of potentially unpublished studies.

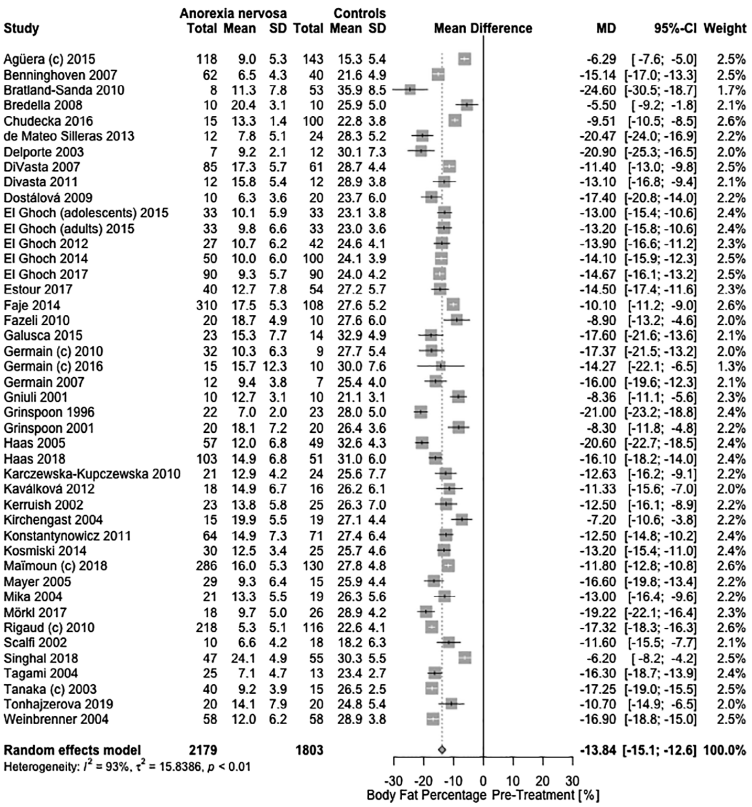

FIGURE 3 Cross-sectional meta-analysis of studies reporting body fat percentage in acutely-ill/pretreatment female AN patients compared with healthy controls. Forty-four samples had the appropriate data for the meta-analysis with 2,179 AN cases and 1,803 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: −13.8%; 95% CI: −15.1, −12.6; $Q = 5.49 \times 10^{-101}$) with the mean differences ranging from −24.6% to −5.5%. Heterogeneity between studies was statistically significant (τ^2 = 15.84; $p = 1.40 \times 10^{-98}$; I^2 = 92.8%). C, subtype-combined sample

$Q = 3.21 \times 10^{-8}$) higher proportion of total body mass. In males, fat-free mass in AN patients was −9.37 kg (95% CI: −12.47, −6.27, $Q = 2.00 \times 10^{-8}$) lower before treatment than in controls. During treatment, female AN patients gained 2.98 kg (95% CI: 1.74, 4.22, $Q = 6.89 \times 10^{-6}$) fat-free mass, resulting in 1.82 kg (95% CI: −2.57, −1.08, $Q = 5.41 \times 10^{-6}$) lower fat-free mass compared to controls. Yet, weight-recovered female individuals with AN still showed 1.27 kg (95% CI: −1.79, −0.75, $Q = 5.49 \times 10^{-6}$) lower fat-free mass than controls.

More specifically, pretreatment fat-free mass of the extremities in females was 1.5% (95% CI: −2.0, −1.0, $Q = 8.84 \times 10^{-9}$) less of total body mass. After treatment, no marked regional differences in fat-free mass were observed in female AN patients. However, weight-recovered female individuals with AN had 0.9% (95% CI: −1.3, −0.5, $Q = 6.30 \times 10^{-5}$) lower trunk fat-free mass of total body mass than controls.

Before treatment, we observed a 393.95 kcal/day (95% CI: −531.04, −256.86, $Q = 6.53 \times 10^{-8}$) lower resting energy expenditure and 4.77 L (95% CI: −6.13, −3.41, $Q = 3.06 \times 10^{-11}$) less total body water in female AN patients, which persisted with 3.71 L (95% CI: −7.07, −0.36, Q = 0.05) after treatment. Both were measured by BIA. However, resting energy expenditure was not corrected for fat-free mass or body mass in the original studies, limiting its interpretability. Before treatment, total body water in females was associated with fat mass ($\beta_{metareg}$ = 0.60, p = .01) and the difference in fat-free mass between AN cases and controls ($\beta_{metareg}$ = 0.48, p = .003).

Before treatment, only the amount of total body water was significantly different between female individuals ($p_{subgroup} = 1.47 \times 10^{-4}$) suffering from the restricting (−5.31 L, 95% CI: −8.15, −2.47, $p_R = 2.47 \times 10^{-4}$, k = 4) or the binge-eating/purging subtype (−11.1 L, 95% CI: −12.04, −10.16, $p_{BP} = 5.06 \times 10^{-119}$, k = 1; Table S3). However, this finding was limited by only one study investigating the binge-eating/purging subtype).

3.5 | Secondary outcome: Bone mineral measures

3.5.1 | Bone mineral content and density

Compared with healthy controls, whole-body bone mineral content in female individuals with AN was 0.16 kg (95% CI: −0.19, −0.12, $Q = 2.73 \times 10^{-20}$) lower before treatment and 0.09 kg (95% CI: −0.13, −0.05, $Q = 1.63 \times 10^{-5}$) lower after treatment. Weight-restored female individuals with AN showed 0.10 kg (95% CI: −0.18, −0.03, Q = 0.01) lower whole-body bone mineral content compared to controls as they gained on average 0.05 kg (95% CI: 0.02, 0.09, Q = 0.01) during treatment. The interpretability of these estimates is limited due to the insufficient follow-up time after weight recovery, exceeding 6 months in only

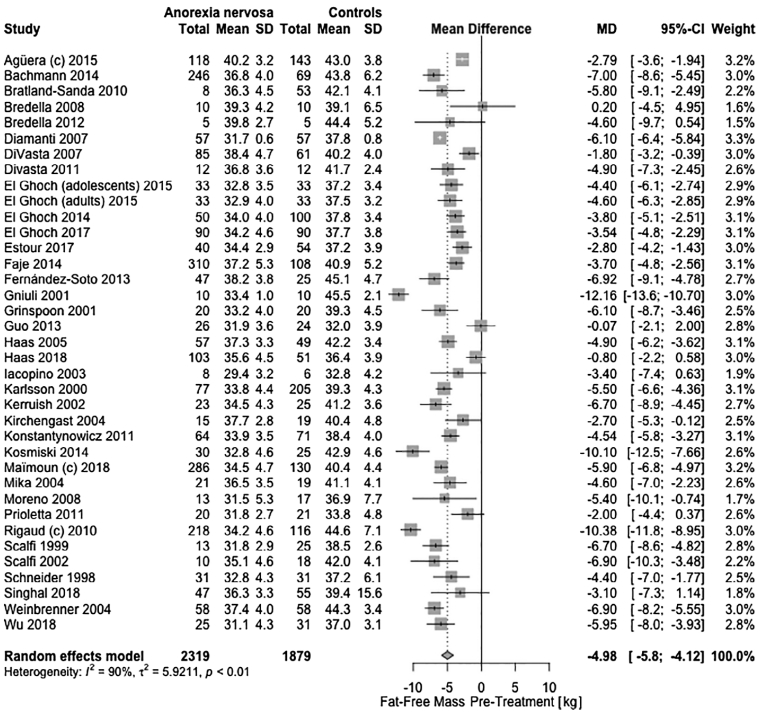

FIGURE 4 Cross-sectional meta-analysis of studies reporting fat-free mass content in acutely-ill/pretreatment female AN patients compared with healthy controls. Thirty-seven samples had the appropriate data for the meta-analysis with 2,319 AN cases and 1,879 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: −4.98 kg; 95% CI: −5.8, −4.1; $Q = 1.99 \times 10^{-28}$) with the mean differences ranging from −12.16 to 0.20 kg. Heterogeneity between studies was statistically significant ($\tau^2 = 5.92$; $p = 1.22 \times 10^{-58}$; $I^2 = 90.5\%$). C, subtype-combined sample

two studies (Dellava et al., 2009; Karlsson et al., 2000). The pretreatment whole-body bone mineral content in females was associated with fat-free mass ($\beta_{metareg} = 0.02$, $p = .02$) and fat mass ($\beta_{metareg} = 0.05$, $p = .02$), as well as the difference in fat mass between AN patients and controls ($\beta_{metareg} = 0.04$, $p = .002$; Table S4). Accordingly, pretreatment whole-body bone mineral density was 0.03 g/cm^2 (95% CI: −0.06, −0.01, $p_{adjCopas} = .02$) lower in females with AN, but our analysis showed a density comparable with healthy controls posttreatment. However, only two studies with 74 AN cases could be included in this analysis.

Before treatment, female AN patients exhibited lower bone mineral density in several regions, including hip, lumbar spine, and femoral neck, with a few being likely to persist after weight recovery. These findings were associated with duration of illness, the age of AN cases, and differences in fat mass between cases and controls (Supporting Information: Secondary Outcomes: Detailed Bone Mineral Measures and Table S4). Cases and controls in our meta-analyses were age- and height-matched (Figures S1 and S6); therefore, these variables are unlikely to be associated with these results.

3.5.2 | Secondary outcomes: Metabolites and hormones

Exploratory results showed that fasting insulin and glucose concentrations were lower in female AN patients compared with controls but not associated with fat or fat-free mass, while lower leptin was associated with fat mass pretreatment. After treatment, these measures returned to concentrations seen in healthy controls. Before treatment, thyroid hormones, cortisol, and IGF-1 were lower in female AN patients, and all three measures were associated with fat mass, whereas higher cortisol in AN patients was associated with fat-free mass. For detailed results, see Supporting Information: Secondary Outcomes: Metabolites and Hormones.

3.5.3 | Methodological moderators

We observed strong between-study heterogeneity (Table 1). To investigate how differences in study design, samples, and measurement methods may influence the primary and secondary outcomes, we performed an additional set of meta-regressions (Tables S4–S7). The method of body composition measurement was associated with pretreatment body fat percentage ($\beta_{DXA} = 3.05$, $p = .01$), fat-free mass ($\beta_{Isotope\ Dilution} = -6.18$, $p = .008$), and fat-free mass percentage ($\beta_{DXA} = -8.28$, $p = .01$), and posttreatment body fat percentage ($\beta_{DXA} = 6.39$, $p = .005$) in females. Furthermore, femoral neck bone mineral density ($\beta_{Outpatient} = -0.12$, $p = 7.65 \times 10^{-4}$) significantly differed between female inpatients and outpatients.

4 | DISCUSSION

Our primary meta-analyses showed marked alterations in body composition traits in patients with AN before and after treatment. Before treatment, all three major body compartments—fat, fat-free, and bone

mass—showed significant reductions that were only partially restored after treatment. Our meta-analysis estimated ~50% lower body fat in AN patients which was mirrored by leptin concentrations (Perry & Shulman, 2018), both of which recovered with treatment. In females, significant differences were observed in body fat distribution after treatment as body fat is primarily stored in the trunk. This distribution pattern may be due to increased insulin sensitivity observed in AN patients (Ilyas et al., 2018) potentially similar to observations in healthy individuals after short-term overfeeding (McLaughlin et al., 2016). We did not detect meaningful or statistically significant differences in body fat distribution in weight-restored patients, indicating potential redistribution occurring over longer term follow-up.

A new finding from our meta-analysis is that lower fat mass in females with AN was correlated with significantly low bone mineral content and density across the whole body. We speculate that the hormonal cross-talk between fat and bone tissue may be influencing this association (El Ghoch et al., 2016; Hawkes & Mostoufi-Moab, 2018), potentially mediated through greater bone marrow adipose tissue observed in AN (Fazeli & Klibanski, 2018; Suchacki & Cawthorn, 2018). Whole-body bone mineral content remained low in weight-recovered individuals with AN. However, as only two studies followed patients for longer than 6 months (Dellava et al., 2009; Karlsson et al., 2000), the duration of follow-up was insufficient to draw firm conclusions because bone mineral mass is slow to normalize. Future studies should be designed to capture long-term changes. In men with AN, fat mass and fat-free mass were lower before treatment than in controls. However, long-term follow-up studies are missing. It has been reported that short-term weight restoration may normalize body composition patterns but could also lead to central adiposity (El Ghoch, Calugi, et al., 2017), but sample sizes of reports of males are very small. Additionally, in our analysis alterations in bone mineral mass did not affect the height of individuals with AN.

Another new finding in our meta-analysis is that we observed a 5 kg lower fat-free mass in female AN patients, which remained lower even after treatment and in weight-recovered AN patients, indicating that current treatment regimens may insufficiently target fat-free mass. Future studies should also assess muscle mass to identify the components of fat-free mass that are most associated with this reduction.

Our secondary outcomes—associations between detailed body composition and laboratory parameters in AN—were difficult to assess as only a few published studies reported both outcomes consistently. Most biochemical alterations were within the range of normal reference values. However, serious alterations can occur in certain individuals with AN that warrant vigilance by clinicians.

Pretreatment fasting insulin and glucose were reduced in AN patients independent of fat mass, but both concentrations normalized following treatment, suggesting that increased insulin sensitivity (Ilyas et al., 2018) may be a temporary state in AN. The relationship between AN and insulin sensitivity should be investigated by euglycemic hyperinsulinemic clamp that showed mixed findings in very small samples (Castillo, Scheen, Jandrain, & Lefèbvre, 1994; Castillo, Scheen, Lefebvre, & Luyckx, 1985; Dostálová et al., 2009; Karczewska-Kupczewska et al., 2010; Pannacciulli et al., 2003; Prioletta et al., 2011; Zuniga-Guajardo, Garfinkel, & Zinman, 1986). This approach is supported by epidemiological associations of AN with type 1 diabetes (Hedman et al., 2018) and its genetic overlap with fasting insulin (Duncan et al., 2017), type 2 diabetes (Watson et al., 2019), and insulin sensitivity (Hübel et al., 2018).

AN was associated with body fat percentage-associated low T_3- and T_4-syndrome pretreatment, whereas thyroid-stimulating hormone concentrations were normal. Associations between fat mass and thyroid hormones have been described before (Kwon et al., 2018); however, sufficiently powered long-term follow-up studies in AN are absent.

Steroid hormone concentrations were altered showing high cortisol, low estradiol, and normal testosterone. Estradiol was negatively associated with fat-free mass, whereas cortisol was positively associated with fat mass. These findings suggest that fat-free mass may be a potential moderator for the return of menses in AN patients and should be further investigated as most research in recovery of menses primarily focused on BMI- or weight-related cutoffs (Misra et al., 2006; Swenne, 2004). Potential reverse causation should also be taken into account where altered estradiol concentrations may precede changes in fat-free mass.

Overall, the meta-analyzed study sample was highly selected and biased as it comprised mostly European females aged between 14 and 31 years, emphasizing the urgent need for studies including diverse ancestries, such as Asia, South and Central America, and Africa. Females and males differ in body composition and metabolic characteristics (Karastergiou & Fried, 2017; Link & Reue, 2017), underscoring the need for more studies on males with AN. Our study selection was limited by the lack of control groups and underreported extensive sample overlap. Moreover, control groups were only measured at baseline in all longitudinal studies, failing to account for age- and growth-related variation, potentially inflating estimates. Furthermore, no clear-cut and consistent definition of recovery from AN was used across studies, contributing to heterogeneity (Murray, Loeb, & Le Grange, 2018). This underscores the necessity of developing standard definitions of remission and recovery in the eating disorders field (Bardone-Cone, Hunt, & Watson, 2018).

Methodologically, we observed effects of either BIA or DXA on the measurement of body composition in AN, questioning the comparability of the two methods. Larger, longitudinal validation studies comparing both methods with whole-body MRI in eating disorders should be conducted. Additional factors influencing body composition and biochemical measures, such as menstrual cycle, diurnal changes, fasting, and preanalytical procedures are summarized in Table 3 and should be carefully assessed in future studies (Hernandes et al., 2017).

Most importantly, blood comprises approximately 3,500 highly correlated and interacting proteins (hupo.org; Schwenk et al., 2017) and 4,600 metabolites (serummetabolome.ca; Psychogios et al., 2011); therefore, the measurement of single proteins, hormones, or metabolites is ill-advised. Metabolomics, proteomics, and lipidomics can capture large amounts of information at adequate statistical power when used in large samples (Hernandes et al., 2017). Additionally, large epidemiological databases that have measured biomarkers in childhood, such as the Avon Longitudinal Study of Parents and

TABLE 3 Minimum requirement of variables that should be assessed, reported, and included in statistical analyses of case–control studies examining anorexia nervosa or other eating disorders to facilitate reproducibility, meta-analysis, and meta-regression

Sampling	Sample characteristics
Cases and controls • Underlying population: community, hospital • Consecutive sample or selection • If consecutive, attrition and reasons • Diagnosis and ascertainment • Diagnostic schema • Independent validation Controls • Repeated measurement at follow-up • Exclusion of current and history of diagnosis (i.e., screening) • Matching (e.g., age, sex) • Exclusion criteria	Cases and controls • Age • Biological sex and gender • Height • Weight • Body mass index • Ancestry • Socioeconomic status & education Cases • Age of onset • Duration of illness
Body composition	**Menstrual status**
• Fat mass • Fat-free mass • Bone mineral content and density • Ideally: Muscle mass • Measurement method: e.g., MRI, DXA, or BIA • Physical activity (ideally accelerometer data)	Cases • Dysmenorrhea or amenorrhea • Duration of amenorrhea • Age of menarche • If menstruating, stage or day of cycle Controls • Stage or day of the menstrual cycle (e.g., follicular phase)
Blood sampling	**Substances**

• Blood sample type whole blood, serum, plasma
• Fasting state
• Fasting period
• The time point of blood sampling
• Pre-analytics
• Storage
• Storage duration
	Dose and duration of
	• Contraceptives
	• Supplements & vitamins
	• Medication
	  ○ Prescription
	  ○ Over the counter
	• Laxatives
	• Illicit drugs
	• Alcohol consumption
	• Smoking behavior

[a]Adapted from Hernandes, Barbas, & Dudzik, 2017. Abbreviations: BIA, bioelectrical impedance analysis; DXA, dual-energy X-ray absorptiometry; MRI, magnetic resonance imaging.

Children (ALSPAC; Golding, Pembrey, Jones, & ALSPAC Study Team, 2001) and Generation R (Kooijman et al., 2016), should be harnessed to determine whether those who go on to develop AN show evidence for premorbid differences in body composition and biochemical parameters as has been observed for BMI by Yilmaz et al. (2019).

5 | CONCLUSIONS

Detailed measurement of body composition with simple methods, such as BIA or DXA, which offers additional information on bone tissue, may help refine our understanding of the nature of AN and its diagnosis. Our meta-analyses showed that all body compartments were markedly altered in AN. Individuals with AN presented with 50% lower fat mass and prolonged recovery periods for fat-free mass and bone mineral content. The core implication of body composition differences are alterations in metabolism, growth, and development. Although results must be interpreted with caution given small samples, we found evidence indicating alterations in fasting insulin, thyroid, sex, and stress hormones in AN, which appeared to partially normalize with weight gain and recovery. Large birth cohorts that collected information on eating disorders along with metabolomic information offer a rich and exciting opportunity for prospective investigations that add to our understanding of body composition and metabolic mechanisms in risk and maintenance of eating disorders.

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CONFLICT OF INTEREST

C.M.B. reports Shire (Scientific Advisory Board member) and Pearson (author, royalty recipient) (unrelated to the content of this manuscript). G.B. has received grant funding from and served as a consultant to Eli Lilly and has received honoraria from Illumina and has served on advisory boards for Otsuka (all unrelated to the content of this manuscript). The remaining authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

C.H., Z.Y., C.M.B., and G.B. designed research; C.H., Z.Y., K.S., L.B., A.H., J.G.G. conducted research; C.H., Z.Y., K.S., L.B., A.H., J.G.G., E.H. provided essential materials; C.H. analyzed data or performed statistical analysis; C.H., Z.Y., L.B., K.S., E.H., G.B., C.M.B. wrote paper; C.H. had primary responsibility for final content. All authors read and approved the final manuscript.

DATA AVAILABILITY

All data and all scripts used for data analysis are available on github.com/topherhuebel/metabcan.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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3 Genome-wide association study identifies eight loci and implicates metabo-psychiatric origins for anorexia nervosa

This chapter, reporting results from a genome-wide association study on anorexia nervosa and follow up investigations, is presented as a published paper. It is an exact copy of this publication.

Watson, H. J., Yilmaz, Z., Thornton, L. M., **Hübel, C.**, Coleman, J. R. I., Gaspar, H. A., … Bulik, C. M. (2019). Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. *Nature Genetics*, *51*(8), 1207–1214.

Supplementary materials for this chapter, as detailed in the text, are attached in **Appendix 3** and in the folder **Chapter 3** on the CD.

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LETTERS

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Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa

Hunna J. Watson et al.*

Characterized primarily by a low body-mass index, anorexia nervosa is a complex and serious illness[1], affecting 0.9–4% of women and 0.3% of men[2–4], with twin-based heritability estimates of 50–60%[5]. Mortality rates are higher than those in other psychiatric disorders[6], and outcomes are unacceptably poor[7]. Here we combine data from the Anorexia Nervosa Genetics Initiative (ANGI)[8,9] and the Eating Disorders Working Group of the Psychiatric Genomics Consortium (PGC-ED) and conduct a genome-wide association study of 16,992 cases of anorexia nervosa and 55,525 controls, identifying eight significant loci. The genetic architecture of anorexia nervosa mirrors its clinical presentation, showing significant genetic correlations with psychiatric disorders, physical activity, and metabolic (including glycemic), lipid and anthropometric traits, independent of the effects of common variants associated with body-mass index. These results further encourage a reconceptualization of anorexia nervosa as a metabo-psychiatric disorder. Elucidating the metabolic component is a critical direction for future research, and paying attention to both psychiatric and metabolic components may be key to improving outcomes.

The previous PGC-ED GWAS (3,495 cases, 10,982 controls) estimated the common genetic variant-based heritability of anorexia nervosa to be around 20%, identified the first genome-wide significant locus and reported significant genetic correlations (r_g) between anorexia nervosa and psychiatric and metabolic/anthropometric phenotypes[10]. These r_g analyses pointed toward metabolic etiological factors, as they are robust to reverse causation, although they could be mediated associations[11] or reflect confounding processes[12]. To advance genomic discovery in anorexia nervosa and further explore genetic correlations, we combined samples from ANGI[8,9], the Genetic Consortium for Anorexia Nervosa (GCAN)/Wellcome Trust Case Control Consortium-3 (WTCCC-3)[13] and the UK Biobank[14], quadrupling our sample size.

Our GWAS meta-analysis included 33 datasets comprising 16,992 cases and 55,525 controls of European ancestry from 17 countries (Supplementary Tables 1–4). We had 80% power to detect an odds ratio of 1.09–1.19 (additive model, 0.9% lifetime risk, $\alpha = 5 \times 10^{-8}$, minor allele frequency (MAF) = 0.05–0.5). Typical of complex-trait GWAS, we observed test statistic inflation ($\lambda = 1.22$) consistent with polygenicity, with no evidence of significant population stratification according to the linkage disequilibrium (LD) intercept and attenuation ratio (Supplementary Note and Supplementary Fig. 1). Meta-analysis results were completed for autosomes and the X chromosome. We identified eight loci that exceeded genome-wide significance ($P < 5 \times 10^{-8}$; Table 1 for loci; Fig. 1 for the Manhattan plot; Supplementary Figs. 2 and 3 for the forest and region plots, respectively). Many loci were near the threshold for significance, and no significant heterogeneity of SNP associations across cohorts was detected ($P = 0.15–0.64$; Supplementary Fig. 2). Conditional and joint analysis (GCTA-COJO)[15] confirmed independence of the lead SNPs within the significant loci (Supplementary Table 5). The eight loci were annotated to identify known protein-coding genes (Supplementary Table 6; Supplementary Table 7 reports a gene search restricted to the single-gene loci). The previously reported PGC-ED genome-wide significant variant (rs4622308)[10] on 12q13.2 did not reach genome-wide significance ($P = 7.02 \times 10^{-5}$); however, between-cohort heterogeneity was apparent ($I^2 = 53.7$; Supplementary Fig. 4 and Supplementary Note). The odds ratio was in the same direction in 22 (67%) of the cohorts ($z = 2.00$, $P = 0.05$, two-tailed test).

Although GWAS findings are informative genome-wide, identifying strong hypotheses about their connections to specific genes is not straightforward. We evaluated three ways to connect anorexia nervosa-associated loci identified by GWAS to genes: regulatory chromatin interactions, relationship to brain expression quantitative trait loci (eQTLs; using a superset of CommonMind[16] and GTEx[17]) and the standard approach of gene location within a GWAS locus. The significant anorexia nervosa-associated loci implicated 121 brain-expressed genes, 74% by location, 55% by adult brain eQTL analysis, 93% by regulatory chromatin interaction and 58 genes by all three methods. Supplementary Figure 5 shows the eight GWAS loci, GENCODE gene models, adult brain regulatory chromatin interactions, brain eQTLs and functional genomic annotations.

Four single-gene loci were confirmed by eQTL analyses, chromatin interaction studies or both. These were the locus-intersecting genes *CADM1* (locus 2, chromosome 11: 114.9–115.4 Mb, Supplementary Fig. 5b), *MGMT* (locus 4, chromosome 10: 131.2–131.4 Mb, Supplementary Fig. 5d), *FOXP1* (locus 5, chromosome 3: 70.6–71.0 Mb, Supplementary Fig. 5e) and *PTBP2* (locus 6, chromosome 1: 96.6–97.2 Mb, Supplementary Fig. 5f). For locus 5, eQTL data implicated a distal gene, *GPR27*. One intergenic locus (locus 7, chromosome 5: 24.9–25.3 Mb, Supplementary Fig. 5g) had no eQTL or chromatin interactions, whereas the other intergenic locus (locus 8, chromosome 3: 93.9–95.0 Mb, Supplementary Fig. 5h) had eQTL connections to *PROS1* and *ARL13B*. Two complex multigenic loci had many brain-expressed genes and dense chromatin and eQTL interactions that precluded identification of any single gene (locus 1, chromosome 3: 47.5–51.3 Mb; locus 3, chromosome 2: 53.8–54.3 Mb, Supplementary Fig. 5a,c). The clearest evidence and connections were for the single-gene loci that intersected with *CADM1*, *MGMT*, *FOXP1* and *PTBP2*, and we conclude that these genes may have a role in the etiology of anorexia nervosa (Supplementary Note).

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Table 1 | Newly associated genome-wide significant loci for anorexia nervosa

Locus	Chromosome	Base-pair region		Lead SNP	Base pair	*P* value	A1/A2	OR	s.e.	Frequency	Type	Number of genes	Nearest gene
		Start	End										
1	3	47,588,253	51,368,253	rs9821797	48,718,253	6.99×10^{-15}	A/T	1.17	0.02	0.12	Multigenic	111	*NCKIPSD*
2	11	114,997,256	115,424,956	rs6589488	115,096,956	6.31×10^{-11}	A/T	1.14	0.02	0.13	Single gene	1	*CADM1*
3	2	53,881,813	54,362,813	rs2287348	54,039,813	5.62×10^{-9}	T/C	1.11	0.02	0.16	Multigenic	13	*ASB3, ERLEC1*
4	10	131,269,764	131,463,964	rs2008387	131,448,764	1.73×10^{-8}	A/G	1.08	0.01	0.33	Single gene	2	*MGMT*
5	3	70,670,750	71,074,150	rs9874207	71,019,750	2.05×10^{-8}	C/T	1.08	0.01	0.49	Single gene	2	*FOXP1*
6	1	96,699,455	97,284,455	rs10747478	96,901,455	3.13×10^{-8}	T/G	1.08	0.01	0.41	Single gene	2	*PTBP2*
7	5	24,945,845	25,372,845	rs370838138	25,081,845	3.17×10^{-8}	G/C	1.08	0.01	0.56	Intergenic	0	*CDH10*
8	3	93,968,107	95,059,107	rs13100344	94,605,107	4.21×10^{-8}	T/A	1.08	0.01	0.54	Intergenic	2	*NSUN3*

The results of the GWAS meta-analysis of anorexia nervosa (16,992 cases and 55,525 controls) are shown, in which eight novel genome-wide significant loci were detected. Chromosome and region (based on hg19) are shown for SNPs with $P<1\times10^{-5}$ and LD-$r^2>0.1$ with the most associated lead SNP, the location of which is given (base pair). A1/A2 refers to allele 1/allele 2. The odds ratio (OR) and s.e. are shown for the association between allele 1 and the phenotype. Frequency indicates the frequency of allele 1 in controls. The number of genes was determined by genomic location, adult brain eQTL, regulatory chromatin interactions and MAGMA gene-wise analysis (see Methods). The nearest gene is the nearest gene within the region of LD 'friends' of the lead variant (LD-$r^2>0.6\pm500$ kb). The meta-analysis was restricted to variants with MAF ≥ 0.01 and information quality (INFO) score ≥ 0.70. All loci were confirmed using forest plots based on consistent direction of effect in the majority of cohorts and using region plots in which neighboring LD friends were required to show a similar effect. Chromosome X was analyzed but had no loci that reached genome-wide significance. Note, although lead variants are annotated to the nearest gene, this does not mean that the gene listed is a causal gene.

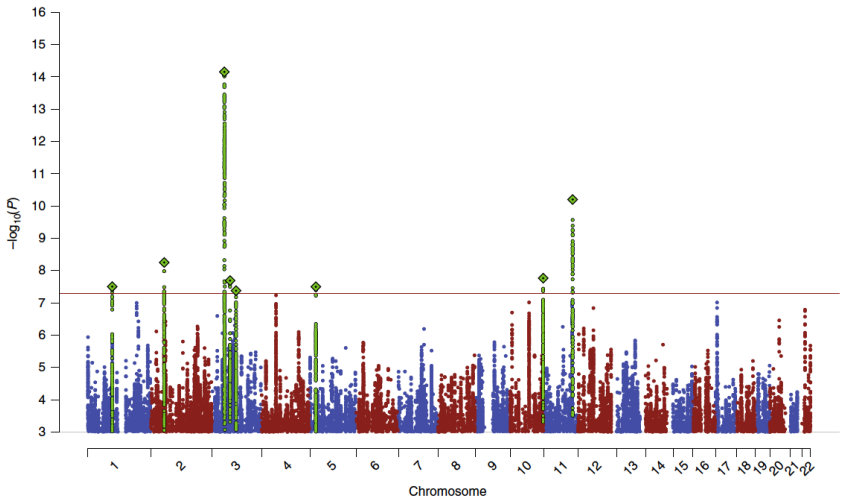

Fig. 1 | The Manhattan plot for the primary genome-wide association meta-analysis of anorexia nervosa with 33 case–control datasets (16,992 cases and 55,525 controls of European descent). The $-\log_{10}(P)$ values for the association tests (two-tailed) are shown on the *y* axis and the chromosomes are ordered on the *x* axis. Eight genetic loci surpassed the genome-wide significance threshold ($-\log_{10}(P)>7.3$; indicated by the line). The lead variant is indicated by a diamond, and green circles show the variants in LD. The blue and red colors differentiate adjacent chromosomes.

Supplementary Table 8 presents multi-trait analysis (GCTA-mtCOJO[18]; conditioning our genome-wide significant SNPs on associated variants in GWAS of body-mass index (BMI), type 2 diabetes, education years, high-density lipoprotein (HDL) cholesterol, neuroticism and schizophrenia. Seven loci appear to be independent. Locus 2 on chromosome 11 may not be unique to anorexia nervosa and may be driven by genetic variation also associated with type 2 diabetes.

Liability-scale SNP heritability (SNP-h^2) was estimated using LD score regression (LDSC)[19,20]. Assuming a lifetime prevalence[2–4] of 0.9–4%, SNP-h^2 was 11–17% (s.e. = 1%), supporting the polygenic nature of anorexia nervosa. Polygenic risk score (PRS) analyses using a leave-one-out approach indicated that the PRS captures approximately 1.7% of the phenotypic variance on the liability scale for discovery $P=0.5$. We did not observe differences in polygenic architecture between anorexia nervosa subtypes with binge eating (2,381 cases, 10,249 controls) or without (2,262 cases, 10,254 controls), or between males (447 cases, 20,347 controls) and females (14,898 cases, 27,545 controls) (Methods, Supplementary Note, Supplementary Fig. 6 and Supplementary Table 9). Similar to females, males in the highest PRS decile had 4.13 (95% confidence interval: 2.58–6.62) times the odds of anorexia nervosa than those

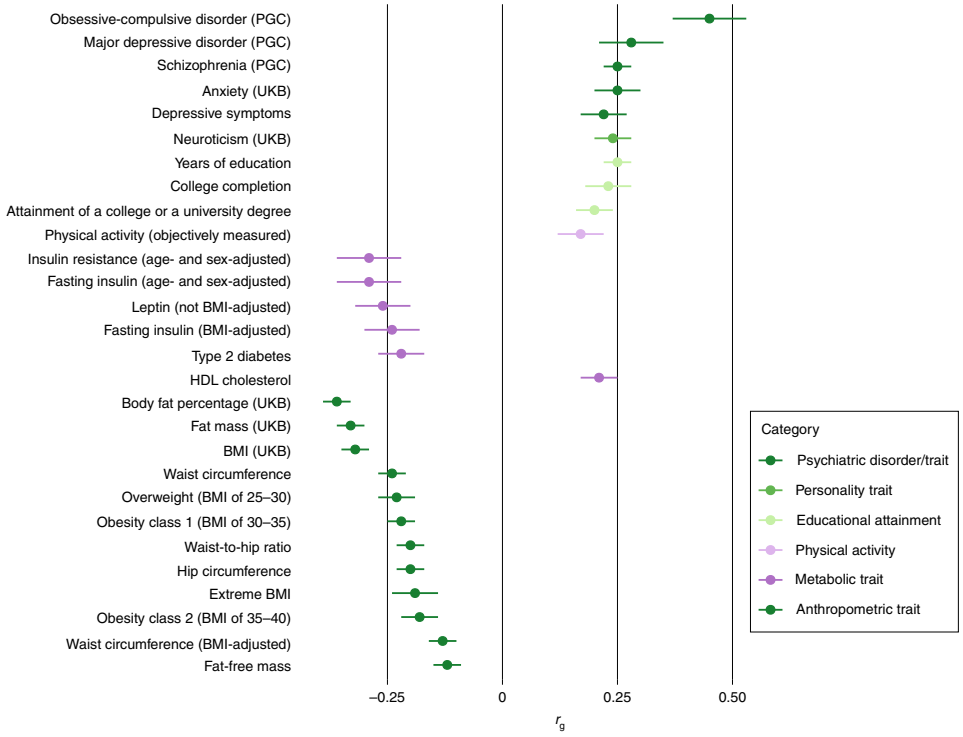

Fig. 2 | Bonferroni-significant genetic correlations (SNP-r_g) between anorexia nervosa and other phenotypes as estimated by LDSC. Only traits with significant *P* values following Bonferroni correction are shown. Error bars show the s.e. Correlations with 447 phenotypes were tested (Bonferroni-corrected significance threshold $P > 1.11 \times 10^{-4}$). Complete results are shown in Supplementary Table 10. Insulin resistance was analysed by the homeostatic model assessment of insulin resistance (HOMA-IR); UKB, UK Biobank.

in the lowest decile. However, confirmation of these results requires larger samples.

We tested SNP-based genetic correlations (SNP-r_g) with external traits using bivariate LDSC[19,20]. Bonferroni-significant SNP-r_g assorted into five trait categories: psychiatric and personality, physical activity, anthropometric traits, metabolic traits and educational attainment (Supplementary Table 10). Figure 2 presents Bonferroni-corrected positive SNP-r_g values associated with obsessive compulsive disorder (SNP-$r_g \pm$ s.e. $= 0.45 \pm 0.08$; $P = 4.97 \times 10^{-9}$), major depressive disorder (0.28 ± 0.07; $P = 8.95 \times 10^{-5}$), anxiety disorders (0.25 ± 0.05; $P = 8.90 \times 10^{-8}$) and schizophrenia (0.25 ± 0.03; $P = 4.61 \times 10^{-18}$). This pattern reflects observed comorbidities in clinical and epidemiological studies[21,22]. The newly identified positive SNP-r_g association with physical activity (0.17 ± 0.05; $P = 1.00 \times 10^{-4}$) encourages further exploration of the refractory symptom of pathologically elevated activity in anorexia nervosa[23]. We note that the significant SNP-r_g of anorexia nervosa with educational attainment (0.25 ± 0.03; $P = 1.69 \times 10^{-15}$) and related constructs was not seen for IQ[24].

Expanding our previous observations[10], we present a number of metabolic and anthropometric r_g with anorexia nervosa that are more pronounced than in other psychiatric disorders. We observed significant negative SNP-r_g with fat mass (-0.33 ± 0.03; $P = 7.23 \times 10^{-25}$), fat-free mass (-0.12 ± 0.03; $P = 4.65 \times 10^{-5}$), BMI (-0.32 ± 0.03; $P = 8.93 \times 10^{-25}$), obesity (-0.22 ± 0.03; $P = 2.96 \times 10^{-11}$), type 2 diabetes (-0.22 ± 0.05; $P = 3.82 \times 10^{-5}$), fasting insulin (-0.24 ± 0.06; $P = 2.31 \times 10^{-5}$), insulin resistance (-0.29 ± 0.07; $P = 2.83 \times 10^{-5}$) and leptin (-0.26 ± 0.06; $P = 4.98 \times 10^{-5}$), and a significant positive SNP-r_g with HDL cholesterol (0.21 ± 0.04; $P = 3.08 \times 10^{-7}$).

Systems biology analyses of our results revealed notable observations (Methods, Supplementary Tables 11–13 and Supplementary Figs. 7–15). Gene-wise analysis with MAGMA prioritized 79 Bonferroni-corrected significant genes, most within the multigenic locus on chromosome 3 (Supplementary Table 11). MAGMA indicated an association with *NCAM1* (Supplementary Table 11), the expression of which increases in response to food restriction in a rodent activity-based anorexia nervosa model[25]. Partitioned heritability analysis showed, as with other GWAS[26], considerable enrichment of SNP-h^2 in conserved regions[27] (fold enrichment = 24.97, s.e. = 3.29, $P = 3.32 \times 10^{-11}$; Supplementary Fig. 7). Cell type group-specific annotations revealed that the overall SNP-h^2 is significantly enriched for tissues of the central nervous system (Supplementary Fig. 8). One biological pathway was significant, Gene Ontology (GO): positive regulation of embryonic development (32 genes, $P = 1.39 \times 10^{-7}$; Supplementary Table 12), which contains two Bonferroni-corrected significant genes on chromosome 3, *CTNNB1* and *DAG1*. *CTNNB1* encodes catenin β-1, which is part of adherens junctions and a component of Wnt signaling, and *DAG1* encodes dystroglycan, a receptor that binds extracellular matrix proteins[28]. *DAG1* falls within locus 1 (47.5–51.3 Mb). This pathway points to a potential role of developmental processes in the etiology of this complex phenotype (although this is currently speculative). Genes associated with anorexia nervosa were enriched for expression in most brain tissues, particularly

the cerebellum, which has a notably high proportion of neurons[29] (Supplementary Fig. 9). Among 24 brain cell types from mouse brain, significant enrichment was found for medium spiny neurons and pyramidal neurons from hippocampal CA1 (Supplementary Fig. 10). Both medium spiny and pyramidal neurons are linked to feeding behaviors, including food motivation and reward[30,31] (Supplementary Note). Using PrediXcan (Supplementary Note), 36 genes were predicted to be differentially expressed in GTEx tissues or blood (Supplementary Table 13), with the expression of *MGMT* predicted to be downregulated in the caudate. We cautiously note that these results represent the first indications of specific pathways, tissues and cell types that may mediate genetic risk for anorexia nervosa.

Because low BMI is pathognomonic of anorexia nervosa, we investigated the extent to which genetic variants associated with BMI accounted for genetic correlations with metabolic and anthropometric traits. First, covarying for the genetic associations of BMI (Methods) led to a mild but statistically non-significant attenuation of the SNP-r_g between anorexia nervosa and fasting insulin, leptin, insulin resistance, type 2 diabetes and HDL cholesterol (Supplementary Tables 14, 15), suggesting that anorexia nervosa shares genetic variation with these metabolic phenotypes that may be independent of BMI. Second, we investigated bidirectional causality using generalized summary data-based Mendelian randomization (GSMR)[18]. This indicated a significant bidirectional causal relationship such that anorexia nervosa risk-increasing alleles may increase the risk for low BMI, and BMI-lowering alleles may increase the risk of anorexia nervosa (Supplementary Table 16). It is important to note that having only eight genome-wide significant loci for anorexia nervosa render this analysis marginally powered in the direction of anorexia nervosa to BMI, although this analysis is well-powered in the direction of BMI to anorexia nervosa.

Replication is challenging with GWAS of low-prevalence conditions, such as anorexia nervosa, as replication samples must be sufficiently powered to detect the initial findings. We included all available samples in our analysis to maximize chances of reaching the GWAS inflection point, after which there might be a linear increase in hits[32]. The PRS leave-one-out analyses provide evidence of replication by demonstrating a higher burden of common risk variants associated with anorexia nervosa cases, compared with controls, across all the cohorts (Supplementary Fig. 16).

In conclusion, we report multiple genetic loci alongside promising clinical and functional analyses and enrichments. The increased sample size in the present GWAS has allowed us to characterize more fully the metabolic contribution to anorexia nervosa than our previous report[10] by revealing significant r_g with metabolism-related phenotypes, including glycemic and anthropometric traits, and by demonstrating that the effect is robust to correction for the effects of common variants significantly associated with BMI. Low BMI has traditionally been viewed as a consequence of the psychological features of anorexia nervosa (that is, drive for thinness and body dissatisfaction). This perspective has failed to yield interventions that reliably lead to sustained weight gain and psychological recovery[7]. Fundamental metabolic dysregulation may contribute to the exceptional difficulty that individuals with anorexia nervosa have in maintaining a healthy BMI (even after therapeutic renourishment). Our results encourage consideration of both metabolic and psychological drivers of anorexia nervosa when exploring new avenues for treating this frequently lethal illness.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, statements of code and data availability and associated accession codes are available at https://doi.org/10.1038/s41588-019-0439-2.

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Author contributions

C.M.B. and P.F.S. conceived and designed the study. L.M.T., C.M.B. and G.B. performed overall study coordination. C.M.B. was the lead principal investigator of ANGI, and P.F.S. was a co-investigator of ANGI. N.G.M., M.L. and P.B.M. were site principal investigators of ANGI. H.J.W., Z.Y., J.R.I.C., C.H., J.B., H.A.G., S.Y., V.M.L., M. Mattheisen, P.G.-R. and S.E.M. performed the statistical analyses. H.J.W., Z.Y., C.H., J.R.I.C., H.A.G., J.B., A.H., P.G.-R., P.F.S., G.B. and C.M.B. comprised the writing group. C.M.B. and G.B. were PGC-ED co-chairs. S. Ripke provided statistical consultation. A.H. assisted with data interpretation. A.W.B., C.M.B., J.J., M.K., K.M.K., P.L., N.G.M., C.N., R.P., L.M.T. and T.D.W. collected and managed the ANGI samples at sites and assisted with site-specific study co-ordination. A.W.B., J.M.B., H.B., S. Crawford, K.A.H., L.J.H., C.J., A.S.K., W.H.K., J.M., C.M.O., J.F.P., N.L.P., M.S., T.W., D.C.W. and D.B.W. provided ANGI controls and extra samples. L.E.D. provided data expertise. S. Gordon, J. Grove, A.K.H., A. Juréus, K.M.K., J.T.L., R.P. and L. Petersen contributed to the ANGI study. S. Gordon, J. Grove, K.K., J.T.L., M. Mattheisen, S. Medland and L. Petersen were ANGI site analysts. K.B.H. and K.L.P. conducted additional secondary analyses. G.W.M., T.D.W., A.B., P.L. and C.N. were ANGI investigators. J.J. and M.K. assisted with ANGI recruitment in New Zealand. PGC-ED members and other individuals contributed to sample acquisition and made individual data from subjects available: R.A.H.A., L.A., T.A., O.A.A., J.H.B., A.W.B., W.H.B., A.B., I.B., C.B., J.M.B., H.B., G.B., K.B., C.M.B., R.B., M. Cassina, S. Cichon, M. Clementi, J.R.I.C., R.D.C., P.C., S. Crawford, S. Crow, J.J.C., U.N.D., O.S.P.D., M.D.Z., G.D., D. Degortes, D.M.D., D. Dikeos, C.D., M.D.W., E.D., K.E., S.E., G.E., T.E., X.E., A. Farmer, A. Favaro, F.F.A., M.M.F., K.F., M. Föcker, L.F., A.J.F., M. Forzan, S. Gallinger, I.G., J. Giuranna, F.G., P.G., M.G.M., J. Grove, S. Guillaume, K.A.H., K.H., J. Hauser, J. Hebebrand, S.G.H., A.K.H., S.H., B.H.D., W.H., A.H., L.J.H., J.I.H., H. Imgart, H. Inoko, V.J., S.J.M., C.J., J.J., A. Julià, G.K., D.K., A.S.K., J.K., L. Karhunen, A.K., M.J.H.K., W.H.K., J.L.K., M.K., A.K., K.K., Y.K., L. Klareskog, G.P.S.K., M.C.L., M.L., S.L.H., R.D.L., P.L., L.L., B.D.L., J. Lissowska, J. Luykx, P.J.M., M. Maj, K. Mannik, S. Marsal, C.R.M., N.G.M., M. Mattheisen, M. Mattingsdal, S. McDevitt, P. McGuffin, A.M., I.M., N.M., J.M., A.M.M., P. Monteleone, P.B.M., M.A.M.C., B.N., M.N., C.N., I.N., C.M.O., J.K.O., R.A.O., L. Padyukov, A.P., J.P., H.P., N.L.P., J.F.P., D.P., R.R., A. Raevuori, N.R., T.R.K., V.R., S. Ripatti, F. Ritschel, M.R., A. Rotondo, D.R., F. Rybakowski, P.S., S.W.S., U.S., A. Schosser, J.S., L.S., P.E.S., M.C.T.S.L., A. Slopien, S.S., M.S., G.D.S., P.F.S., B.Ś., J.P.S., I.T., E.T., A. Tortorella, F.T., J.T., A. Tsitsika, M.T.N., K.T., A.A.V.E., E.V.F.E., T.D.W., G.W., E. Walton, H.J.W., T.W., D.C.W., E. Widen, D.B.W., S. Zerwas and S. Zipfel.

Competing interests

O.A.A. received a speaker's honorarium from Lundbeck. G.B. received grant funding and consultancy fees in preclinical genetics from Eli Lilly, consultancy fees from Otsuka and has received honoraria from Illumina. C.M.B. is a grant recipient from Shire Pharmaceuticals and served on Shire Scientific Advisory Board; she receives author royalties from Pearson. D.D. served as a speaker and on advisory boards, and has received consultancy fees for participation in research from various pharmaceutical industry companies including: AstraZeneca, Boehringer, Bristol Myers Squibb, Eli Lilly, Genesis Pharma, GlaxoSmithKline, Janssen, Lundbeck, Organon, Sanofi, UniPharma and Wyeth; he has received unrestricted grants from Lilly and AstraZeneca as director of the Sleep Research Unit of Eginition Hospital (National and Kapodistrian University of Athens, Greece). J.I.H. has received grant support from Shire and Sunovion, and has received consulting fees from DiaMentis, Shire, and Sunovion. A.S.K. is a member of the Shire Canadian BED Advisory Board and is on the steering committee for the Shire B/educated Educational Symposium: 15–16 June 2018. J.L.K. served as an unpaid member of the scientific advisory board of AssurexHealth Inc. M.L. declares that, over the past 36 months, he has received lecture honoraria from Lundbeck and served as scientific consultant for EPID Research Oy, but has received no other equity ownership, profit-sharing agreements, royalties or patents. P.F.S. is on the Lundbeck advisory committee and is a Lundbeck grant recipient; he has served on the scientific advisory board for Pfizer, has received a consultation fee from Element Genomics, and a speaker reimbursement fee from Roche. J.T. has received an honorarium for participation in an EAP meeting and has received royalties from several books from Routledge, Wiley and Oxford University Press. T.W. has acted as a lecturer and scientific advisor to H. Lundbeck A/S. All other authors have no conflicts of interest to disclose.

Additional information

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Methods

Samples and study design. Thirty-three datasets with 16,992 cases of anorexia nervosa and 55,525 controls were included in the primary GWAS. We included individuals from the PGC-ED Freeze 1[10], newly collected samples from the ANGI[8,9], archived samples from the GCAN/WTCCC3[13], samples from cases of anorexia nervosa from the UK Biobank[14], and additional controls from Poland. Case definitions established a lifetime diagnosis of anorexia nervosa via hospital or register records, structured clinical interviews, or online questionnaires based on standardized criteria (Diagnostic and Statistical Manual of Mental Disorders (DSM) III-R, DSM-IV, International Classification of Diseases (ICD) 8, ICD-9 or ICD-10), whereas in the UK Biobank, cases self-reported a diagnosis of anorexia nervosa. Controls were carefully matched for ancestry, and some, but not all, control cohorts were screened for lifetime eating and/or some or all psychiatric disorders. Given the relative rarity of anorexia nervosa, large unscreened control cohorts were deemed appropriate for inclusion[33].

The cohorts are described in the Supplementary Note. Ethical approvals and consent forms were reviewed and archived for all participating cohorts (see Supplementary Note for Danish methods). Summary details about ascertainment (Supplementary Table 2), the genotyping platforms used (Supplementary Table 3) and genotype availability (Supplementary Table 4) are provided.

Statistical analysis. Data processing and analysis were done on the Lisa Compute Cluster hosted by SURFsara (http://www.surfsara.nl) and the GenomeDK high-performance computing cluster (http://genome.au.dk).

Meta-analysis of genome-wide association data. Quality control, imputation, GWAS and meta-analysis followed the standardized pipeline of the PGC, Ricopili (Rapid Imputation Consortium Pipeline). Ricopili versions used were 2017_Oct_11.002 and 2017_Nov_30.003. Quality control included SNP and sample quality control, population stratification and ancestry outliers, and familial and cryptic relatedness. Further information about the Ricopili pipeline is available from the website (https://sites.google.com/a/broadinstitute.org/ricopili) and GitHub repository (https://github.com/Nealelab/ricopili/tree/master/rp_bin). Further details of the quality control procedures can be found in the Supplementary Note.

Imputation. Imputation of SNPs and insertions–deletions was based on the 1000 Genomes Phase 3 (http://www.internationalgenome.org) data[34].

GWAS. GWASs were conducted separately for each cohort using imputed variant dosages and an additive model. Covariates nominally associated with the phenotype in univariate analysis ($P < 0.05$) and five ancestry principal components were included in the GWAS (Supplementary Table 18). These analyses used the tests and methods programmed in the Ricopili pipeline. To the extent that national laws and regulations permitted, we examined sample overlap across cohorts by performing LD score bivariate regressions and estimating genetic covariance intercepts to assess sample overlap[19,20] (Supplementary Table 19). Genomic inflation factors (λ) of the final datasets indicated no evidence of inflation of the test statistics due to population stratification or other sources (Supplementary Table 1). The 33 cohorts were meta-analyzed with the Ricopili pipeline, which uses an inverse-variance weighted fixed-effect model. We filtered our GWAS results with MAF ≥ 0.01 and INFO score ≥ 0.70 (indicating 'high quality').

Analysis of chromosome X. Several cohorts in the primary GWAS did not have X chromosome variant data, specifically, some GCAN-based cohorts (fre1, ukd1, usa1, gns2) and were excluded. Imputation was performed separately from the autosomes[35]. Chromosome X variants in the pseudoautosomal regions were excluded before imputation. SNPs exceeding MAF and INFO score thresholds of 0.01 and 0.70 were retained and analysis was performed with PLINK v1.9 (https://www.cog-genomics.org/plink2) and Ricopili.

Female-only GWAS. A supplementary GWAS analysis was conducted on females only to determine the similarity of the results to the primary GWAS analysis, which included both females and males. The cohorts that did not have chromosome X variants to verify sex could not be included (fre1, ukd1, usa1, gns2).

Distance- and LD-based clumping. The GWAS results implicate genomic regions (loci). To define a locus, first SNPs that met the genome-wide significant threshold of $P < 5 \times 10^{-8}$ were identified. Second, clumping was used to convert significant SNPs to regions. The SNP with the smallest P value in a genomic window was kept as the index SNP and SNPs in high LD with the index SNP defined the left and right end of the region (SNPs with $P < 0.0001$ and $r^2 > 0.1$ within 3-Mb windows). Third, partially or wholly overlapping clumps within 50 kb were identified and merged into one region. Fourth, only loci with additional evidence of association from variants in high LD as depicted by regional plots were retained; furthermore, forest plots needed to confirm the associations based on the majority of cohorts. Finally, conditional analyses were conducted to identify SNPs with associations independent of the top SNP within the genomic section of interest.

Annotation. Genome-wide significant loci were annotated with RegionAnnotator (https://github.com/ivankosmos/RegionAnnotator) to identify known protein-coding genes within loci (Supplementary Table 6).

Conditional and joint analyses. Conditional and joint analyses were conducted using GCTA-COJO[15]. GCTA-COJO investigates every locus with a joint combination of independent markers using a genome-wide SNP selection procedure. It takes into account the LD correlations between SNPs and runs a conditional and joint analysis on the basis of conditional P values. After a model optimizing process, the joint effects of all selected SNPs are calculated. The largest subsample from our GWAS (sedk) was used to approximate the underlying LD structure of the investigated lead SNPs. The conditional regression was performed in a stepwise manner using the GCTA software[36]. We analyzed SNPs that had $P < 5 \times 10^{-8}$ (Supplementary Table 5).

Multi-trait-based conditional and joint analyses. To separate marginal effects from conditional effects (that is, the effect of a risk factor on an outcome controlling for the effect of another risk factor), we performed a multi-trait-based conditional and joint analysis (GCTA-mtCOJO)[18] using an extension of the GCTA software (http://cnsgenomics.com/software/gcta)[36] (Supplementary Table 8). This method uses summary-level data to perform the conditional analysis. We conditioned the results of our anorexia nervosa GWAS on GWAS results for education years[37], type 2 diabetes[38], HDL cholesterol[39], BMI (C.H. et al., manuscript in preparation), schizophrenia[40] and neuroticism[41]. We again used the individual-level genotype data from our largest cohort (sedk) to approximate the underlying LD structure. As a first step, the method performs a generalized summary data-based Mendelian randomization (GSMR) analysis (http://cnsgenomics.com/software/gsmr) to test for causal association between the outcome (that is, anorexia nervosa) and the risk factor (for example, schizophrenia). We removed potentially pleiotropic SNPs from this analysis by the heterogeneity in dependent instruments (HEIDI) outlier method[18]. Pleiotropy is the phenomenon when a single locus directly affects several phenotypes. The power of the HEIDI outlier method is dependent on the sample size of the GWAS. Pleiotropic SNPs are defined as the SNPs that show an effect on the outcome that significantly diverges from that expected under a causal model. Second, the GCTA-mtCOJO method calculates the genetic correlation between the exposure and the outcome using LDSC (https://github.com/bulik/ldsc) to adjust for genetic overlap[19,20]. It also uses the intercept of the bivariate LDSC to account for potential sample overlap[19,20]. As a result, GCTA-mtCOJO calculates conditional betas, conditional standard errors and conditional P values. Subsequently, we clumped the conditional GWAS results using the standard PLINK v.1.9[42] algorithm (SNPs with $P < 0.0001$ and $r^2 > 0.1$ within 3-Mb windows) to investigate whether any of the genome-wide significant loci showed dependency on genetic variation associated with other phenotypes. As described previously[18], the GCTA-mtCOJO analysis requires the estimates of b_{xy} of the covariate risk factors on the target risk factor and disease, r_g of the covariate risk factors, heritability (h^2_{SNP}) for the covariate risk factors and the sampling covariance between SNP effects estimated from potentially overlapping samples.

eQTL and chromosome conformation capture (Hi-C) interactions. Although GWAS findings are informative genome-wide, identifying strong hypotheses about their connections to specific genes is not straightforward. The lack of direct connections to genes constrains subsequent experimental modeling and efforts to develop improved therapeutics. Genomic location is often used to connect significant SNPs to genes, but this is problematic because GWAS loci usually contain many correlated and highly significant SNP associations over hundreds of kilobases. Moreover, the three-dimensional arrangement of chromosomes in cell nuclei enables regulatory interactions between genomic regions that are located far apart[43]. Chromosome conformation capture methods, such as Hi-C, enable identification of three-dimensional interactions in vivo[44,45] and can clarify GWAS findings. For example, an intergenic region associated with multiple cancers was shown to be an enhancer for *MYC* through a long-range chromatin loop[46,47], intronic *FTO* variants are robustly associated with body mass but influence expression of distal genes through long-range interactions[48], and Hi-C was used previously[49] to assess the three-dimensional chromatin interactome in fetal brain and connections of some schizophrenia associations to specific genes were found in the study.

To gain a better understanding of the three-dimensional organization of chromatin in the brain and to evaluate disease relevance, we applied Hi-C[50] to post-mortem samples ($n = 3$ samples of the adult temporal cortex). Details on methodology, data processing, quality control and statistical models used for these analyses have been published elsewhere[51]. We generated sufficient reads to enable a kilobase-resolution map of the chromatin interactome from adult humans. We generated tissue RNA-sequencing, total-stranded RNA-sequencing, chromatin immunprecipitation followed by sequencing (H3K27ac, H3K4me3 and CTCF) and open chromatin data (assay for transpose-accessible chromatin using sequencing; ATAC-seq) for the adult brain to help to interpret the Hi-C results. We also integrated brain expression and eQTL data from GTEx to aid these analyses. The Hi-C analysis is unbiased in that all chromatin interactions that pass a confidence threshold are considered when evaluating the associations between SNPs and genes (that is, it is not a capture experiment where only candidate SNP-to-gene associations are evaluated).

Similar to a previous study[49], we used Hi-C data generated from human adult brain to identify genes implicated by three-dimensional functional interactomics

(Supplementary Fig. 5). These Hi-C data ($n = 3$, anterior temporal cortex) contain more than 103,000 high-confidence, regulatory chromatin interactions[51]. These interactions capture the physical proximity of two regions of the genome in brain nuclei (anchors, 10 kb resolution), although they are separated by 20 kb to 2 Mb in genomic distance. We focused on the regulatory subset of E–P or P–P (E, enhancer; P, promoter) chromatin interactions (with P defined by the location of an open chromatin anchor near the transcription start site of an adult brain-expressed transcript and E defined by the overlap with open chromatin in adult brain plus either H3K27ac or H3K4me3 histone marks). The presence of a regulatory chromatin interaction from a GWAS locus to a gene provides a strong hypothesis about SNP-to-gene regulatory functional interactions.

SNP-based heritability estimation. LDSC software (https://github.com/bulik/ldsc) and methods were used to estimate SNP-based heritabilities for each cohort and overall[19,20]. We used precomputed LD scores based on the 1000 Genomes Project European ancestry samples[34] (directly downloaded from https://github.com/bulik/ldsc). The liability scale estimate assumed a population prevalence of 0.9–4% for anorexia nervosa[2,3].

Polygenic risk scoring for within-trait predictions. Polygenic leave-one-dataset-out analysis, using PRSice v2.1.3[52], was conducted in the first instance to identify any extreme outlying datasets. In addition, it enabled the evaluation of the association between anorexia nervosa PRS and anorexia nervosa risk in an independent cohort as a means of replication of the GWAS results. We derived a PRS for anorexia nervosa from the meta-analysis of all datasets except for the target cohort, and then applied the PRS to the target cohort to predict affected status (Supplementary Fig. 16). Logistic regression was performed, including as covariates the first five ancestry components and any other principal components that were significantly associated with the phenotype in the target cohort, and the target cohort was split into deciles based on anorexia nervosa PRS, for which decile 1, which consisted of those with the lowest anorexia nervosa PRS, served as the reference.

Anorexia nervosa subtype analysis. PRS analyses were conducted with anorexia nervosa subgroups to investigate prediction of case status across the subtypes. For this, we split the cases of anorexia nervosa into two groups based on whether binge eating was present. First, GWAS meta-analyses were conducted for anorexia nervosa with binge eating compared to controls (2,381 cases and 10,249 controls; $k = 3$ datasets: aunz, chop, usa2) and anorexia nervosa with no binge eating compared to controls (2,262 cases and 10,254 controls; $k = 3$ datasets: aunz, chop, usa2). Controls were randomly split between analyses to maintain independence (Supplementary Fig. 6). Genetic correlation analysis using LDSC[19,20] was conducted to examine the potential genetic overlap of the two anorexia nervosa subtypes (Supplementary Table 9). Second, using PRSice[52], we calculated PRS for each anorexia nervosa subtype separately in the three target cohorts for which anorexia nervosa subtype data were available. Finally, mean PRS scores were estimated for each subtype by cohort after accounting for covariates in R. Subtype phenotyping is described in the Supplementary Note.

Males. To assess whether sex-specific differences in genetic risk load exist for anorexia nervosa, we calculated PRS, using PRSice[52], from a GWAS meta-analysis performed on females only (14,898 cases and 27,545 controls) and applied it to a male-only target cohort (447 cases and 20,347 controls) to predict affected status.

Genetic correlations in the cross-trait analysis. Common variant-based genetic correlation (SNP-r_g) analysis measures the extent to which two traits or disorders share common genetic variation. SNP-r_g between anorexia nervosa and 447 traits (422 from an internally curated dataset and 25 from LDHub[53]) were tested using GWAS summary statistics using an analytical extension of LDSC[19,20]. The sources of the summary statistics files (PMID, DOI or unpublished results) used in the LDSC are provided in Supplementary Table 10. When there were multiple summary statistics files available for a trait, significant SNP-r_g reported in the main text were chosen based on the largest sample size and/or matching ancestry with our sample (that is, European ancestry).

Genetic correlations with anorexia nervosa corrected for BMI were carried out to investigate whether the observed genetic correlations between anorexia nervosa and metabolic phenotypes were attributable to BMI or partially independent. We used GCTA-mtCOJO[18] to perform a GWAS analysis for anorexia nervosa conditioning on BMI using BMI summary data from our UK Biobank analysis (described in the next section) to derive anorexia nervosa GWAS summary statistics corrected for the common variants genetic component of BMI (Supplementary Tables 14, 15).

GWAS of related traits in UK Biobank. Several GWAS analyses were carried out for traits using data from the UK Biobank to allow us to investigate body composition genetics in healthy individuals without a psychiatric or weight-altering disorder or individuals who were taking weight-altering medication. We also used UK Biobank data to carry out GWAS of physical activity level, anxiety and neuroticism (Supplementary Table 20). For details, see the Supplementary Note.

GSMR analyses. We performed two bidirectional GSMR analyses[18] to test for the causal association first between BMI and anorexia nervosa, and second between type 2 diabetes and anorexia nervosa, using an extension of the GCTA software[36] (Supplementary Table 16). We used the individual-level genotype data from our largest cohort (sedk) to approximate the underlying LD structure. We removed potentially pleiotropic SNPs from this analysis by the HEIDI outlier method[18]. Pleiotropic SNPs are defined as the SNPs which show an effect on the outcome that significantly diverges from the one expected under a causal model. The method uses the intercept of the bivariate LD score regression to account for potential sample overlap[19,20]. As a rule of thumb, GSMR requires GWAS to have at least ten genome-wide significant hits. We lowered the threshold for this requirement to eight SNPs in our analyses of anorexia nervosa as an exposure and BMI or type 2 diabetes as an outcome. Results, therefore, should be interpreted with caution. Moreover, we investigated bidirectional conditional effects between BMI or type 2 diabetes and anorexia nervosa. We used GCTA-mtCOJO to perform a GWAS analysis for anorexia nervosa conditioning on BMI using summary data from our UK Biobank analysis or type 2 diabetes using summary data[38]. Our anorexia nervosa GWAS and the BMI and type 2 diabetes GWAS analyses are based on independent samples. For BMI, we also reran the GSMR analysis using the BMI-adjusted anorexia nervosa GWAS summary data from the GCTA-mtCOJO analysis.

Gene-wise analysis. MAGMA v.1.06[54] (http://ctg.cncr.nl/software/magma) was used to perform a gene-wise test of association with anorexia nervosa based on GWAS summary statistics. MAGMA generates gene-based *P* values by combining SNP-based *P* values within a gene while accounting for LD. To include regulatory regions, SNPs are mapped to genes within a 35-kb upstream and 10-kb downstream window, and the gene *P* value is obtained using the multi = snp-wise model, which aggregates mean and top SNP association models. We tested 19,846 ENSEMBL genes, including the X chromosome (Supplementary Table 11). As a reference panel for the underlying LD structure, we used 1000 Genomes European data phase 3[34].

Pathway analysis. MAGMA v.1.06[54] was used to perform a competitive pathway analysis, testing whether genes associated with anorexia nervosa were more enriched in a given pathway than all other pathways. The analysis included chromosome X. Biological pathways were defined using gene ontology pathways and canonical pathways from MSigDB v.6.1[55], and psychiatric pathways mined from the literature. A total of 7,268 pathways were tested (Supplementary Table 12).

Partitioned heritability. Partitioned heritability was investigated using stratified LDSC[26], which estimates the per-SNP contribution to overall SNP-heritability (SNP-h^2) across various functional annotation categories of the genome (Supplementary Fig. 7). It accounts for linked markers and uses a 'full baseline model' of 24 annotations that are not specific to any cell type. We excluded the MHC region in our analysis. SNP-h^2 can be partitioned in two different ways: a non-cell type-specific and a cell type-specific manner. Partitioned heritability analysis was used to test for cell type-specific enrichment in the GWAS of anorexia nervosa among 10 cell type groups: adrenal tissue and pancreas, cardiovascular tissue, central nervous system, connective tissue and bone, gastrointestinal tissue, immune and hematopoietic tissues, kidney, liver, skeletal muscle and other tissues, which includes adipose tissue (Supplementary Fig. 8).

Gene expression. We conducted a series of gene expression analyses as described in the Supplementary Note.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

The policy of the PGC is to make genome-wide summary results public. Genome-wide summary statistics for the meta-analysis are freely downloadable from the website of the PGC (http://www.med.unc.edu/pgc/results-and-downloads). Individual-level data are deposited in dbGaP (http://www.ncbi.nlm.nih.gov/gap) for ANGI-ANZ/SE/US (accession number phs001541.v1.p1) and CHOP/PFCG (accession number phs000679.v1.p1). ANGI-DK individual-level data are not available in dbGaP owing to Danish laws, but are available through collaboration with principal investigators of the Danish institutions. GCAN/WTCCC3 individual-level data are deposited in EGA (https://www.ebi.ac.uk/ega) (accession number EGAS00001000913) with the exception of the Netherlands and USA/Canada; data from these countries are available through collaboration with principal investigators of institutions in these countries. UK Biobank individual-level data can be applied for on the UK Biobank website (http://www.ukbiobank.ac.uk/register-apply).

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4 Genomics of body fat percentage may contribute to sex bias in anorexia nervosa

This chapter, investigating sex differences in genetic correlations of body composition, metabolic and psychiatric traits with anorexia nervosa, is presented as a published paper. It is an exact copy of this publication.

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Supplementary materials for this chapter, as detailed in the text, are attached in **Appendix 4** and in the folder **Chapter 4** on the CD.

Full author lists for each consortium are available in **Appendix 6**.

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RESEARCH ARTICLE

Genomics of body fat percentage may contribute to sex bias in anorexia nervosa

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Anorexia nervosa (AN) occurs nine times more often in females than in males. Although environmental factors likely play a role, the reasons for this imbalanced sex ratio remain unresolved. AN displays high genetic correlations with anthropometric and metabolic traits. Given sex differences in body composition, we investigated the possible metabolic underpinnings of female propensity for AN. We conducted sex-specific GWAS in a healthy and medication-free subsample of the UK Biobank (n = 155,961), identifying 77 genome-wide significant loci associated with body fat percentage (BF%) and 174 with fat-free mass (FFM). Partitioned heritability analysis showed an enrichment for central nervous tissue-associated genes for BF%, which was more prominent in females than males. Genetic correlations of BF% and FFM with the largest GWAS of AN by the Psychiatric Genomics Consortium were estimated to explore shared genomics. The genetic correlations of $BF\%_{male}$ and $BF\%_{female}$ with AN differed significantly from each other ($p < .0001$, $\delta = -0.17$), suggesting that the female preponderance in AN may, in part, be explained by sex-specific anthropometric and metabolic genetic factors increasing liability to AN.

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KEYWORDS

eating disorder, fat-free mass, female, genetic correlation, GWAS, shared genetics

1 | INTRODUCTION

Anorexia nervosa (AN) is one of the most lethal psychiatric disorders and has established environmental and genetic risk factors (Chesney, Goodwin, & Fazel, 2014; Keshaviah et al., 2014). Female sex is the most robust and replicated risk factor, with nine females affected for each male case observed (Bulik et al., 2006; Micali, Hagberg, Petersen, & Treasure, 2013; Steinhausen & Jensen, 2015). Although historic diagnostic criteria for AN may have favored detection in females (e.g., presence of the amenorrhea criterion), most schemata did allow for the diagnosis of AN in males (American Psychiatric Association, 2013; World Health Organization, 1992). The focus of most work on gender differences in AN has been on sociocultural factors, such as personal evaluation of physical appearance and social pressures to be thin (Bakalar, Shank, Vannucci, Radin, & Tanofsky-Kraff, 2015) although models based on biological and hormonal factors, such as growth, sex, and appetite-regulating hormone abnormalities have also been posited (Culbert, Racine, & Klump, 2016; Schorr & Miller, 2017). However, collectively findings to date are not yet able to account for the widely disparate prevalences by sex.

The marked alterations in body composition, including fat mass (FM), fat-free mass (FFM), and bone mineral density observed in AN are clinical characteristics of the illness, but have generally been considered to be sequelae of starvation (Westmoreland, Krantz, & Mehler, 2016). Females with AN show significantly greater FM deficits than affected males (Nagata et al., 2017) and, even after recovery, some individuals do not restore healthy body fat percentages (BF%; El Ghoch, Calugi, Lamburghini, & Dalle Grave, 2014). Moreover, lower BF % is a major risk factor for relapse (Bodell & Mayer, 2011). The causes of these particular sex differences have not yet been fully investigated.

Both AN and body composition as measured by bioelectrical impedance analysis are heritable (Schousboe et al., 2004; Tarnoki et al., 2014; Table S1). Significant negative single nucleotide polymorphism-based autosomal genetic correlations (*SNP-*r_g) between AN and body mass index (BMI) and BF% were observed by the largest GWAS of AN conducted by the Eating Disorders Working Group of the Psychiatric Genomics Consortium (PGC-ED; Duncan et al., 2017; Watson et al., 2018). This suggests shared etiology between those anthropometric traits and AN. Furthermore, AN shares common genetic variation with metabolic traits, such as insulin sensitivity and cholesterol. This revealed, for the first time, that a component of the genetic risk for AN is related to body composition and metabolism (Duncan et al., 2017; Hinney et al., 2017).

Phenotypic sex differences in body composition are also present in the general population; discernible as early as adolescence, females have on average higher BF% (Flegal et al., 2009), and less visceral adipose tissue and FFM than males (Paus, Wong, Syme, & Pausova, 2017), partially due to differences in adipocyte metabolism (Cheung & Cheng, 2016; Karastergiou & Fried, 2017; Link & Reue, 2017). Moreover, epidemiological findings indicate a female predominance at both tails of BMI, in extreme obesity (Kelly, Yang, Chen, Reynolds, & He, 2008; Lovre & Mauvais-Jarvis, 2015) and in AN (Steinhausen & Jensen, 2015). Recent evidence shows clear biological sex differences in metabolism in rodent models (Arnold, 2017) and in humans (Mauvais-Jarvis, 2015).

The observed phenotypic sex differences in body composition across the lifespan are partially due to genetic factors (Table S1 and Figure S1; Silventoinen et al., 2016, 2017). Heritability estimates from twin studies (*twin-*h^2) of these epidemiological sex differences unveiled that *twin-*h^2 estimates of BMI—a proxy of BF%—vary across the lifespan and show sex-specific patterns, most apparent at the age of 13 years, from 20 to 30, and between ages 70 and 80 (Table S1 and Figure S1; Silventoinen et al., 2016, 2017). Although the *twin-*h^2 varies somewhat, the specific genetic factors influencing BMI remain stable from decade to decade postadolescence, whereas environmental effects appear to change across time, especially in females (Haberstick et al., 2010). Additionally, several GWAS of proxy measures of BF% (Heid et al., 2010; Lindgren et al., 2009; Pulit et al., 2018; Randall et al., 2013; Winkler et al., 2017) and of BF% itself (Kilpeläinen et al., 2011; Lu et al., 2016) show clear sex differences in genome-wide significant genomic loci and documented female-specific heterogeneity in the genomic architecture extensively (for review, see Link & Reue, 2017; Pulit, Karaderi, & Lindgren, 2017; Small et al., 2018). Furthermore, studies have shown that BMI GWAS show tissue-specific enrichment for the central nervous system (CNS; Finucane et al., 2015, 2018), whereas waist-to-hip ratio adjusted for BMI GWAS showed enrichment for adipose tissue (Finucane et al., 2018).

Convergent epidemiological and genetic findings show that the regulation of body composition varies between the sexes and is substantially influenced by both genetic and environmental factors. The primary goal of this study is to investigate whether a sex-specific analysis of genetic determinants of body composition may partially explain the observed female preponderance in AN. We utilize new GWAS summary statistics from the PGC-ED with about 16,000 cases, capitalizing on the availability of detailed and highly standardized body composition measurements and genetic data of 155,961 healthy and medication-free individuals in the UK Biobank. Together, these provide a unique opportunity for a powerful investigation of the sex specificity of the genetic underpinnings of body composition and psychiatric traits and their relationship with AN.

2 | METHODS

2.1 | Genome-wide association study of AN by the Eating Disorders Working Group of the Psychiatric Genomics Consortium

The meta-analysis of GWAS on AN was a combined effort by the AN Genetics Initiative (Kirk et al., 2017; Thornton et al., 2018) and the

PGC-ED (www.med.unc.edu/pgc) and comprised 33 cohorts from 17 countries (Table S3) with 16,992 AN cases and 55,525 controls (Watson et al., 2018). The GWAS included 72,358 females (16,531 of whom are cases) and 24,454 males (460 of whom are cases; Table S2). The analysis includes additional samples from the Genetic Consortium for AN, the Wellcome Trust Case Control Consortium 3 (Boraska et al., 2014), and the UK Biobank (Sudlow et al., 2015). Case definitions established a lifetime diagnosis of AN via hospital or register records, structured clinical interviews, or online questionnaires based on standardized criteria—DSM-III-R, DSM-IV, ICD-8, ICD-9, or ICD-10—(American Psychiatric Association, 2013; World Health Organization, 1992), whereas in the UK Biobank cases self-reported a diagnosis of AN (Davis et al., 2018). Quality control, imputation, GWAS, and meta-analysis followed the standardized pipeline of the PGC, Rapid Imputation Consortium Pipeline (Ricopili; https://github.com/Nealelab/ricopili/tree/master/rp_bin). SNPs were excluded if they had a minor allele frequency (MAF) smaller than 1%, if no call was made in more than 2% of samples following imputation, if they were imputed with low confidence (INFO<0.7), or if they deviated substantially from Hardy–Weinberg equilibrium (controls $p < 10^{-6}$, cases $p < 10^{-10}$). Individuals were excluded if they showed inbreeding coefficients >0.2, or evidence of DNA contamination. Ancestry outliers were removed based on plotting of the first two principal components (PCs). The analysis was performed using imputed variant dosages and an additive model. The SNP-based heritability (*SNP-h*^{2}) of AN calculated using these data was 17% (*SE* = 1%), suggesting that a substantial fraction of the heritability of AN stems from common genetic variation across all autosomes (Watson et al., 2018).

2.2 | GWASs of body composition: Study design and participants

Our study includes a cross-sectional analysis of the baseline data from the epidemiological resource UK Biobank (www.ukbiobank.ac.uk; Allen, Sudlow, Peakman, Collins, & UK Biobank, 2014; Sudlow et al., 2015). To identify genetic variation associations with BF% and FFM that are not confounded by illnesses and their downstream effects or metabolism-changing medication, we applied stringent exclusion criteria (Table S2). Due to this trait-specific medication and illness filtering, the final analysis included 155,961 (45% female) healthy and drug-free European ancestry participants comprising 32% of the genotyped UK Biobank participants. European ancestry was defined by 4-means clustering of the first two PCs from the genetic data (Warren et al., 2017). Phenotypic characteristics separated by sex are presented in Table 1. All statistics were calculated in R 3.4.1 if not otherwise stated.

2.3 | Body composition assessment in healthy participants

Body composition was assessed with a rigorous and highly standardized protocol by UK Biobank using the same Tanita BC-418 MA machines (Tanita Corporation, Arlington Heights, IL) for every participant. This body composition analyzer calculates FFM and FM from raw bioelectrical impedance data, using standard formulas including sex, age, height, and athleticism. Individuals whose hydration status might be compromised (e.g., suffering from diabetes mellitus or other endocrine diseases) were excluded (Table S3). Bioelectrical impedance technology has been extensively validated (Genton et al., 2003; Kyle et al., 2004; Lu et al., 2016), and results in more reliable estimates of body adiposity than BMI for healthy individuals (Mazzoccoli, 2016; Tanamas et al., 2016). Therefore, bioelectrical impedance analysis is the most feasible method in very large epidemiological samples, such as the UK Biobank, compared with proxy measures of adiposity, and does not expose participants to radiation unlike dual-energy X-ray absorptiometry.

TABLE 1 Phenotypic characteristics of individuals in the analyses

	Meta-analyzed	Female	Male
Number (%)	155,961	70,700 (45%)	85,261 (55%)
Age (years)	54.9 ± 8.1	54.8 ± 8.0	55.0 ± 8.2
Height (cm)	170.4 ± 9.3	163.0 ± 6.2	176.4 ± 6.7
Weight (kg)	78.1 ± 15.1	69.6 ± 12.6	85.1 ± 13.2
BMI (kg/m^2)	27.0 ± 4.2	26.2 ± 4.6	27.4 ± 3.8
Waist circumference (cm)	89.4 ± 12.6	82.3 ± 11.3	95.3 ± 10.3
Hip circumference (cm)	102.5 ± 8.1	102.0 ± 9.3	103.0 ± 6.9
Waist-to-hip ratio	0.9 ± 0.1	0.8 ± 0.1	0.9 ± 0.1
Body fat (%)	29.3 ± 8.2	35.3 ± 6.7	24.4 ± 5.5
Fat mass (kg)	23.0 ± 8.5	25.3 ± 9.1	21.2 ± 7.5
FFM (kg)	55.1 ± 11.6	44.4 ± 4.6	63.9 ± 7.4
SES, Townsend deprivation index	−1.6 ± 2.9	−1.7 ± 2.8	−1.7 ± 2.9

BMI = body mass index; FFM = fat-free mass; SES = socioeconomic status.
Data are *n* (%), or mean (*SD*).

2.4 | GWASs on body composition

We calculated sex-specific GWAS on residualized BF% and FFM, using BGENIE v1.2 (Bycroft et al., 2018). Our final analyses included 7,794,483 SNPs and insertion–deletion variants with an MAF >1%, imputation quality scores >0.8, and that were genotyped, or present in the Haplotype Reference Consortium (HRC) reference panel used for imputation by UK Biobank (McCarthy et al., 2016). We used an additive model on the imputed dosage data provided by UK Biobank, and residualized phenotypes prior to GWAS for factors related to assessment center, genotyping batch, smoking status, alcohol consumption, menopause, and for continuous measures of age, and socioeconomic status (SES) measured by the Townsend deprivation index (Townsend, 1987) as independent variables. We accounted for underlying population stratification by also including the first six PCs, calculated on the genotypes of the European subsample. We then meta-analyzed these sex-specific GWAS using METAL (http://csg.sph.umich.edu/abecasis/metal/; Willer, Li, & Abecasis, 2010) using an inverse variance weighted model with a fixed effect, to obtain sex-combined results. Significantly associated SNPs ($p < 5 \times 10^{-8}$) were considered as potential index SNPs. SNPs in LD ($r^2 > 0.2$) with a more strongly associated SNP within 3,000 kb were assigned to the same locus using Functional Mapping and Annotation (FUMA; Watanabe, Taskesen, van Bochoven, & Posthuma, 2017). Overlapping clumps additionally were merged with a second clumping procedure in FUMA merging all lead SNPs with $r^2 = 1$ to genomic loci. After clumping, independent genome-wide significant loci (5×10^{-8}) were compared with entries in the NHGRI-EBI

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GWAS catalog (MacArthur et al., 2017) using FUMA (Watanabe et al., 2017). Sex-specific loci are defined as reaching genome-wide significance (5×10^{-8}) in either females or males while not showing at least suggestive significance in the opposite sex (5×10^{-6}) with differences in beta estimates that remain significant after Bonferroni correction for the total number of significant genomic loci.

2.5 | Genome-wide SNP-based heritability and partitioned heritability

Using BOLT-LMM (Loh et al., 2015) on genotyped, genome-wide, common genetic variants and linkage disequilibrium score regression (LDSC) implemented in LDSC v.1.0.0 (Bulik-Sullivan et al., 2015) on genome-wide summary statistics, we calculated the total phenotypic variance explained by common autosomal SNPs, SNP-based heritability (*SNP-*h^2). We included all genotyped and imputed autosomal variants for BF% and FFM and used the LD score reference files provided with the software. We tested for differences between the heritabilities by calculating *SE* using a block jackknife method implemented into the software. To identify tissue types associated with BF% and FFM, we performed a partitioned heritability analysis in LDSC v.1.0.0, ranking 10 cell type groups based on contribution to heritability after controlling for the effects of 53 functional annotations (Finucane et al., 2015).

2.6 | Genetic correlations

Using an analytic extension of LDSC (Bulik-Sullivan et al., 2015), we calculated SNP-based bivariate genetic correlations (*SNP-*r_g) across the autosomes to examine the genetic overlap between AN and metabolic and psychiatric GWAS summary statistics. First, we calculated *SNP-*r_gs between anthropometric traits, namely our BF% and FFM GWASs with GWASs of childhood BMI (~8 years; Felix et al., 2016), childhood obesity (Bradfield et al., 2012), childhood FFM (Medina-Gomez et al., 2017), adult FFM (Zillikens et al., 2017), and adolescence and young adulthood BMI (~15–25 years; Graff et al., 2013), to estimate the genomic overlap of body composition between different periods of life. Second, we calculated *SNP-*r_gs of these anthropometric traits across the lifespan with AN.

Additionally, we computed *SNP-*r_gs of AN (Supporting Information) with glycemic traits, such as insulin sensitivity assessed by the insulin resistance homeostatic model assessment (HOMA-IR), fasting glucose, and insulin concentrations (Lagou, Mägi, & Hottenga, 2018; Manning et al., 2012; Scott et al., 2012), to investigate potential mediation of the relationship between body fat and AN. Physical activity is reported to be increased in AN patients (Achamrah, Coëffier, & Déchelotte, 2016; Shroff et al., 2006); therefore, we estimated the genetic overlap between physical activity (Hanscombe, 2018, Unpublished, Supporting Information) and AN. We explored the genomic contribution to the comorbidity of AN with psychiatric disorders and traits, including major depressive disorder (MDD; Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium et al., 2013), anxiety (Purves et al., 2017), schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium et al., 2014), obsessive–compulsive disorder (OCD; International Obsessive Compulsive Disorder Foundation Genetics Collaborative (IOCDF-GC) and OCD Collaborative Genetics Association Studies (OCGAS), 2018), and neuroticism (Coleman, 2017, Unpublished, Supporting Information), as well as educational attainment (Okbay et al., 2016) by calculating *SNP-*r_gs. Information on all GWAS is presented in Table S4.

2.7 | Sex-specific analyses of genomic determinants

We investigated differences between sexes in heritability and genetic architecture to identify sex-specific liability driven by genomic factors. We examined differences (δ) in the *SNP-*h^2 estimates between males and females using a block jackknife approach (Supporting Information) and tested whether the *SNP-*r_gs between females and males were different from 1 to identify potential genetic differences related to sex. We calculated the *SNP-*r_g of the female and male GWASs with AN separately to investigate the differences in the relationship of these sex differences with the risk for AN. To test the statistical significance of all estimates, we calculated their *SE* and corresponding *p* value by applying a block jackknife method, as described and implemented in LDSC v1.0.0 by Bulik-Sullivan et al. (2015) and in our Supporting Information.

As a sensitivity analysis, we repeated all *SNP-*r_g analysis with a female-only GWAS of AN. However, due to the small number of male AN cases, it was impossible to perform a male-only analysis. All methods are described in more detail in the Supporting Information. Stringent multiple testing correction was performed on each analysis, using matrix decomposition to detect the effective number of tests and subsequent Bonferroni correction of the *p* value thresholds.

3 | RESULTS

3.1 | GWAS of AN

The AN GWAS resulted in eight genome-wide significant loci and showed enrichment for CNS cell types. It genetically correlated with a broad range of metabolic and psychiatric phenotypes, mirroring clinically observed comorbidity (for details, see Duncan et al., 2017 ; Watson et al., 2018).

3.2 | GWAS of body composition measures in the UK Biobank

After quality control, we performed sex-stratified association analyses on the continuous outcomes of BF% and FFM. Minimal inflation due to population stratification or other systematic biases was indicated by LDSC intercepts between 1.02 and 1.10 and lambda median statistic inflation values (λ_{median}) between 1.18 and 1.59 (Table S4 and Figure S3a,b). We identified 34 independent loci associated with meta-analyzed BF% that are not reported to be associated with anthropometric traits in the GWAS catalog (MacArthur et al., 2017) and replicated 42 independent genome-wide significant results ($p < 5 \times 10^{-8}$) after LD-based and distance-based clumping (Figure 1, Figure S4a, Table S5a,b). We identified one male-specific locus in BF% (Table S5a). The meta-analyzed GWAS of FFM yielded 83 novel loci and replicated 78 genomic risk loci previously associated with anthropometric traits (Figure 2, Figure S3b, Table S6a,b). We identified 13 male-specific

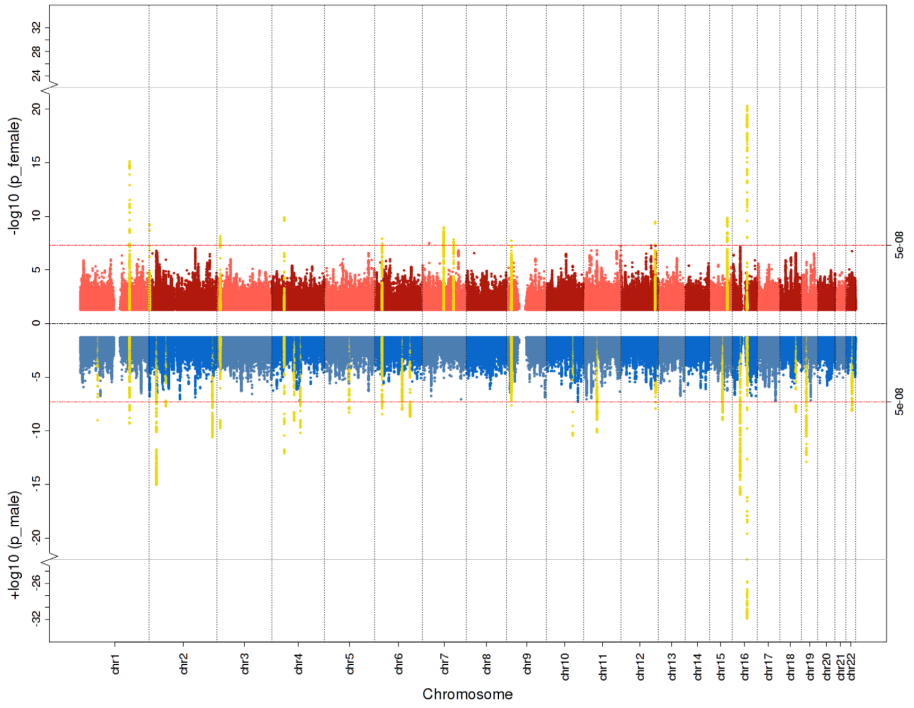

FIGURE 1 Miami plot for female (red), male (blue), and meta-analyzed (yellow) genome-wide body fat percentage (BF%) associations. Significant loci from the sex-combined analyses are highlighted in yellow if they also reached genome-wide significance in the sex-specific genome-wide association studies (GWASs). The genome-wide significance threshold $p < 5 \times 10^{-8}$ is represented by the red horizontal lines.
Chr = chromosome

genomic loci in FFM (Table S6a). All genomic regions, region plots thereof, their annotations, including nearby protein coding genes (within 100 kb), and previous entries in the GWAS catalog are published on FUMA (http://fuma.ctglab.nl/browse) entries 20–25. Summary statistics are available for download www.topherhuebel.com/GWAS.

3.3 | Genome-wide SNP-based and partitioned heritability

The *SNP-h*^{2} for BF% ranged between 29 and 33%, and for FFM between 43 and 51% (Figure 3), while that for AN is about 17–20% with an assumed population prevalence of 0.9% (Duncan et al., 2017; Watson et al., 2018). The *SNP-h*^{2} of FFM_{male} measured by LDSC was significantly higher than the *SNP-h*^{2} of FFM_{meta} ($p < .001$, δ*SNP-h*^{2} = 5.6%). However, neither the *SNP-h*^{2} estimates for BF% nor for FFM measured by LDSC differed significantly between the sexes.

Partitioned heritabilities can estimate the proportion of the overall *SNP-h*^{2} that can be attributed to different cell type groups. $BF\%_{female}$ showed an significant enrichment for the CNS cell type group with 14% of SNPs explaining an estimated 40% of the *SNP-h*^{2} ($p = .004$), whereas $BF\%_{male}$ was significantly enriched for the "other" cell type group that contains adipose tissue with 20% of SNPs explaining an estimated 57% of the *SNP-h*^{2} ($p = .004$; Figure S4a,b). The FFM_{female} and FFM_{male} were enriched for connective and bone tissue with 11% of SNPs explaining an estimated 47% of *SNP-h*^{2} in both sexes ($p_{female} = 6.65 \times 10^{-6}$; $p_{male} = 2.29 \times 10^{-7}$; Figure S5a,b). The meta-analyzed FFM_{both} was also enriched for skeletal muscle with 10% of SNPs explaining an estimated 37% of *SNP-h*^{2} ($p = .004$, Figure S5c).

3.4 | Genetic correlations of anthropometric traits across the lifespan

The significant *SNP-r*$_g$ between $BF\%_{meta}$ and $BMI_{childhood}$ was 0.46 (*SE* = 0.04; $p = 6.11 \times 10^{-32}$) and between $BF\%_{meta}$ and $BMI_{adolescence/young\ adulthood}$ was 0.48 (*SE* = 0.05; $p = 9.24 \times 10^{-25}$). Similarly, $FFM_{childhood}$ and $FFM_{adulthood}$ showed a significant *SNP-r*$_g$ of 0.69 (*SE* = 0.10; $p = 2.70 \times 10^{-12}$) and $FFM_{childhood}$ also correlated genetically with FFM_{meta} in our UK Biobank sample (*SNP-r*$_g$ = 0.30; *SE* = 0.04; $p = 3.24 \times 10^{-12}$).

$BF\%_{meta}$ and FFM_{meta} correlated genetically (*SNP-r*$_g$ = 0.26; *SE* = 0.02; $p = 3.95 \times 10^{-26}$). The *SNP-r*$_g$ between $BF\%_{female}$ and $BF\%_{male}$ was significantly less than 1 (*SNP-r*$_g$ = 0.89, *SE* = 0.03; $p_{=1} = .0005$), indicating heterogeneity in the genomic architecture between females and males (Figure 4).

3.5 | Sex-specific genetic correlations with AN

We calculated *SNP-r*$_g$ between the sex-specific and sex-combined GWAS with AN to investigate sex differences. The genetic correlation

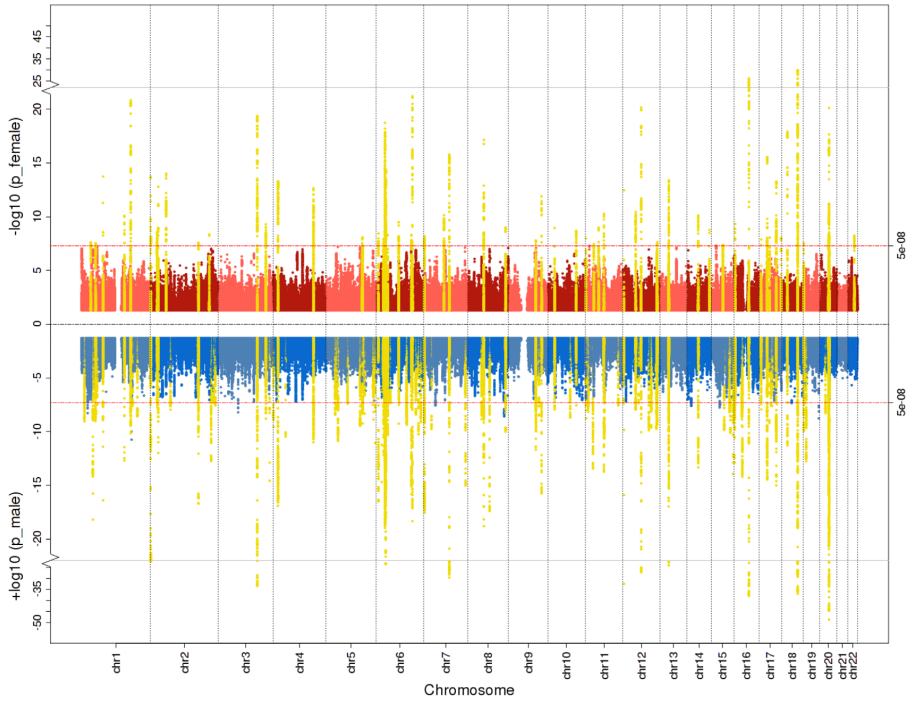

FIGURE 2 Miami plot for female (red), male (blue), and meta-analyzed (yellow) genome-wide fat-free mass (FFM) associations. Significant loci from the sex-combined analyses are highlighted in yellow if they also reached genome-wide significance in the sex-specific genome-wide association studies (GWASs). The genome-wide significance threshold $p < 5 \times 10^{-8}$ is represented by the red horizontal lines.
Chr = chromosome

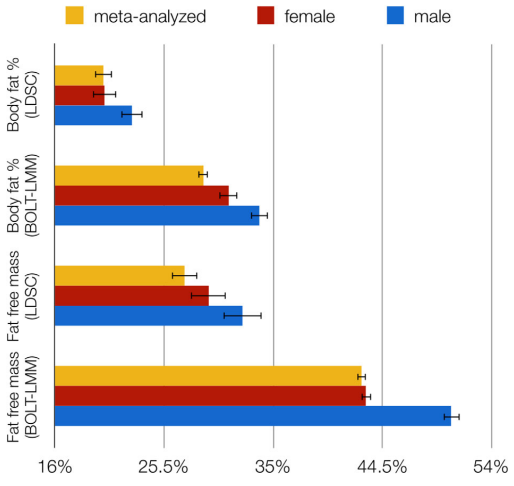

FIGURE 3 Sex-specific single nucleotide polymorphism-based heritability estimates (*SNP-h*^{2}) for body fat percentage and fat-free mass calculated by BOLT-LMM (Loh et al., 2015) and linkage disequilibrium score regression (LDSC; Bulik-Sullivan et al., 2015). Error bars represent *SE*. All estimated *SNP-h*^{2} were statistically significant

between BF%$_{female}$ and AN was −0.44 (*SE* = 0.04; $p = 8.28 \times 10^{-27}$), whereas that between BF%$_{male}$ and AN was −0.26 (*SE* = 0.04; $p = 1.04 \times 10^{-13}$). These *SNP-r*$_g$ were significantly different from each other (δ*SNP-r*$_g$ = −0.17; *SE* = 0.04; $p = 4.23 \times 10^{-5}$). AN showed a significant genetic correlation with FFM$_{meta}$ (*SNP-r*$_g$ = −0.14; *SE* = 0.03; $p = 5.79 \times 10^{-6}$) Physical activity$_{female}$ showed a significant *SNP-r*$_g$ with AN (*SNP-r*$_g$ = 0.25; *SE* = 0.06; $p = 1.10 \times 10^{-5}$), but physical activity$_{males}$ did not (*SNP-r*$_g$ = 0.10; *SE* = 0.06; *p* = .07). However, this difference was not statistically significant (δ*SNP-r*$_g$ = −0.13; *SE* = 0.07; *p* = .05; Figure 4) after multiple testing correction.

BMI-adjusted fasting insulin concentrations and AN were genetically correlated (*SNP-r*$_g$ = −0.24; *SE* = 0.06; $p = 2.31 \times 10^{-5}$). Fasting insulin$_{female}$ was genetically correlated with AN (*SNP-r*$_g$ = −0.36; *SE* = 0.07; $p = 5.29 \times 10^{-7}$), but not fasting insulin$_{male}$ (*SNP-r*$_g$ = −0.16; *SE* = 0.05; *p* = .003). However, this difference in *SNP-r*$_g$ between sexes did not reach significance (δ*SNP-r*$_g$ = −0.19; *SE* = 0.08; *p* = .02) after multiple testing correction. Sex- and age-adjusted insulin resistance (HOMA-IR) correlated significantly with AN (*SNP-r*$_g$ = −0.29, *SE* = 0.07; $p = 2.83 \times 10^{-5}$; Figure 5), but no sex differences were observed.

AN was significantly correlated with MDD$_{female}$ (*SNP-r*$_g$ = 0.26; *SE* = 0.07; $p = 4.00 \times 10^{-4}$) and anxiety$_{meta}$ (*SNP-r*$_g$ = 0.25; *SE* = 0.05; $p = 8.90 \times 10^{-8}$). However, the difference between the male and female *SNP-r*$_g$ with AN was not significant in MDD (δ*SNP-r*$_g$ = −0.004;

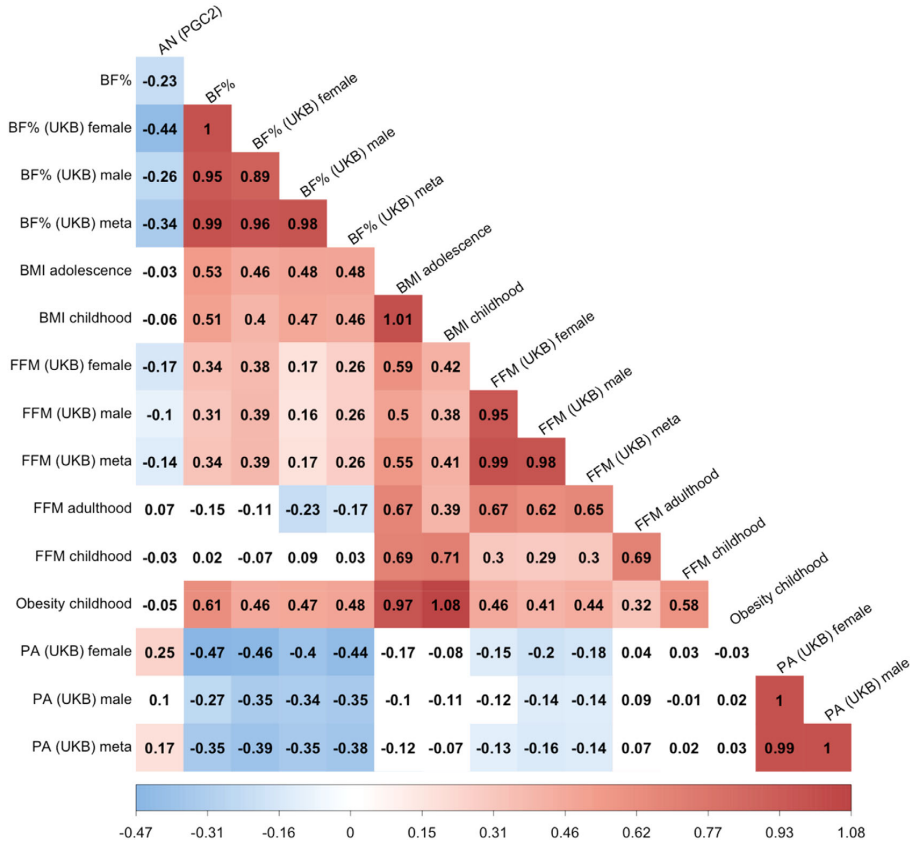

FIGURE 4 Heatmap of sex-specific bivariate single nucleotide polymorphism-based genetic correlations (*SNP*-r^2_g) of body fat percentage, BMI, fat-free mass, physical activity, and obesity with AN. The strength of the correlation is reflected in the hue. Blue colors are negative *SNP*-r_gs, meaning that the same genetic variants influence both traits in opposite directions, and red are positive *SNP*-r_gs meaning that the same genetic variants influence traits in the same direction. Colored squares are significant after correction for multiple comparisons by matrix decomposition and Bonferroni correction ($p_{Bonferroni}$ = .05/10). The *SNP*-r_gs were calculated by linkage disequilibrium score regression (LDSC). AN = anorexia nervosa; BF% = body fat percentage; BMI = body mass index; FFM = fat-free mass; PA = physical activity; PGC2 = 2nd freeze psychiatric genomics consortium; UKB = UK Biobank

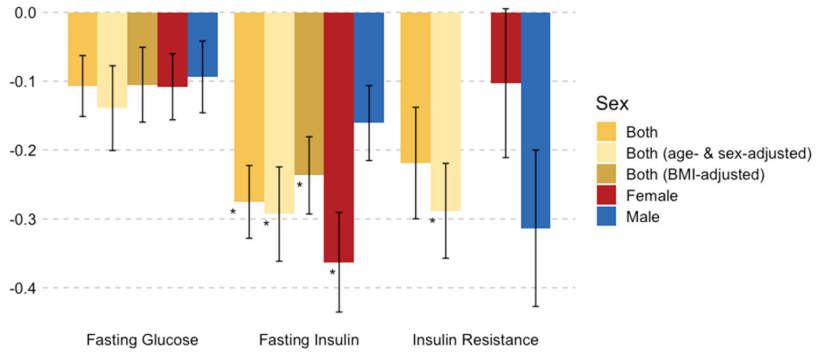

FIGURE 5 Sex-specific bivariate single nucleotide polymorphism-based genetic correlations (*SNP*-r_g) of fasting glucose, fasting insulin, and insulin resistance assessed by the HOMA-IR with AN. The *SNP*-r_gs were calculated by linkage disequilibrium score regression (LDSC). Significant *SNP*-r_gs are marked with an asterisk (*) after correction for multiple comparisons by matrix decomposition and Bonferroni correction ($p_{Bonferroni}$ = .05/28). The error bars depict the *SE*. Summary statistics for BMI-adjusted HOMA-IR were not available. AN = anorexia nervosa; BMI = body mass index; HOMA-IR = insulin resistance by homeostatic model assessment

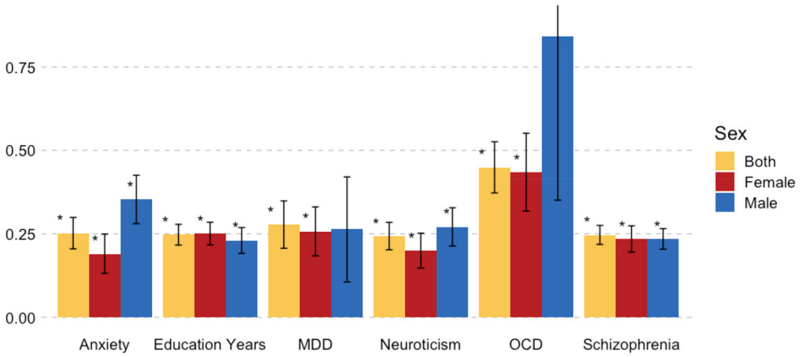

FIGURE 6 Sex-specific bivariate single nucleotide polymorphism-based genetic correlations (*SNP-r_g*) of probable anxiety disorder (anxiety), education years, MDD, neuroticism, OCD, and schizophrenia with anorexia nervosa. The *SNP-r_g*s were calculated by linkage disequilibrium score regression (LDSC). Significant *SNP-r_g*s are marked with an asterisk (*) after correction for multiple comparisons by matrix decomposition and Bonferroni correction ($p_{Bonferroni}$ = .05/28). The error bars depict the *SE*. The *SE* of the OCD_{male} reaches above 1 and has been cut off. MDD = major depressive disorder; OCD = obsessive–compulsive disorder

SE = 0.16; *p* = .98). While the *SNP-r_g* between education years in females and males was significantly different from 1 (*SNP-r_g* = 0.91, *SE* = 0.02; $p = 7.99 \times 10^{-5}$), indicating sex differences, the *SNP-r_g* of education years with AN did not differ between females and males (*δSNP-r_g* = −0.02; *SE* = 0.03; *p* = .59; Figure 6). As sensitivity analysis, all *SNP-r_g*s were also calculated with a female only AN GWAS showing no meaningful differences (Table S8a).

4 | DISCUSSION

The latest GWAS on AN by the PGC-ED presented evidence for a reconceptualization of AN as a metabo-psychiatric disorder by identifying significant *SNP-r_g*s of AN with a variety of metabolic phenotypes, including body composition, lipid metabolism, and glycemic traits (Duncan et al., 2017; Watson et al., 2018). We extended the findings on the relationship between BF% and AN by replicating that genomic effects on BF% differ by sex (Heid et al., 2010; Lindgren et al., 2009; Pulit et al., 2018; Randall et al., 2013; Winkler et al., 2017) and showing that female-specific effects on BF% have a significantly greater genetic correlation with AN (*SNP-r_g* = −0.44; *SE* = 0.04; $p = 8.28 \times 10^{-27}$) than male-specific effects on BF% (*SNP-r_g* = −0.26; *SE* = 0.04; $p = 1.04 \times 10^{-13}$). This suggests that a specific set of genomic variation may be differentially active in females and may increase the liability for AN. The partitioned heritability analyses of *SNP-h^2* showed that $BF\%_{female}$ was significantly enriched for CNS tissue while $BF\%_{male}$ was enriched for adipose tissue, recapitulating prior findings in sex-combined samples (Finucane et al., 2015, 2018; Willer et al., 2009). This indicates a sex-specific enrichment for BF% and that BF% has associated genetic variation underlying its biology thereby validating the use of bioelectrical impedance analysis to measure body compartments. Moreover, our findings suggest that different tissues may be implicated in the regulation of BF% in females and males.

In our analysis of body composition across the lifespan, $BF\%_{childhood}$, $BF\%_{adolescence\ and\ young\ adulthood}$, and $FFM_{childhood}$ were not genetically correlated with AN, whereas $BF\%_{adult}$ and FFM_{adult} was. However, GWASs of BF% and BMI as well as FFM were well correlated across the lifespan with *SNP-r_g*s of about ~0.60 across childhood, adolescence, young adulthood, and adulthood (Figure 4). This suggests that a proportion of BF%-associated genomic variation may become operative at a later age and that this component may be correlated with risk for AN. This seems to overlap with the period—between 20 and 30 years of age—in which females and males show a significant difference in the *twin-h^2* of BMI (Figure S1; Silventoinen et al., 2016, 2017).

Additionally, we estimated *SNP-r_g* of AN with sex-specific GWASs of physical activity and glycemic traits to investigate potential moderators and mediators of the relationship between body fat and AN. Only $physical\ activity_{female}$ and $fasting\ insulin_{female}$ were significantly genetically associated with AN. However, the differences between female and male *SNP-r_g*s were only nominally significant for both traits and did not survive correction for multiple testing emphasizing the need for larger sample sizes to examine sex differences.

In our sex-specific investigation of the contribution of psychiatric disorders and behavioral traits to AN, genomic variation associated with MDD in females and OCD in males suggested a possible sex effect in their *SNP-r_g* with AN, but statistical tests did not confirm this. Power may be an issue; in particular, the current sample size of the OCD GWAS is relatively small. Consequently, some of our findings need to be interpreted cautiously, and this analysis should be repeated after much larger GWASs are available preferably with >10,000 cases of each sex. Some GWASs, however, are well powered and although the *SNP-r_g* of education years between males and females was significantly lower than 1—similar to BF%—we did not observe sex differences in the *SNP-r_g* of education years with AN, suggesting that metabolic traits may be more likely to contribute to the sex-specific liability to AN than psychiatric or behavioral phenotypes.

Our investigation was limited by the small proportion of male AN cases in the primary AN GWAS (Table S2) not allowing for male-only analyses. However, female-only analyses did not show meaningful differences to the sex-combined analyses (Table S8a). We were unable to include the X chromosome in the investigations as the genotype or summary level data for several GWASs in the PGC AN GWAS

meta-analysis were not available to us when the analyses were conducted. However, this should be incorporated in future studies. Most importantly, compared with prior BMI GWAS, our study benefited from arguably more homogeneously assessed body composition phenotypes, allowing us to differentiate between BF% and FFM more effectively (Kilpeläinen et al., 2011; Lu et al., 2016). Moreover, we adjusted for smoking behavior, alcohol consumption, and menopause and excluded participants taking weight altering medications and participants with somatic diseases or psychiatric disorders that affect body composition, such as cancers, diabetes, and MDD. This is a unique and important feature of our investigation and substantially reduced possible confounding of our GWAS.

Conclusion

Our results add further evidence that AN is both a psychiatric and metabolic disorder and suggest that an age-dependent specific set of genomic variation may be differentially active in females that influences body composition, which may also contribute to liability for AN. Our work could have therapeutic implications, by considering exploring approaches to using body composition measures or genetic markers of body composition as predictors of clinical course or adverse outcome, and as a component of personalized treatment that considers an individual's propensity to lose therapeutically restored weight. Some individuals may be at greater risk of relapse, for example, when confronted with periods of negative energy balance, and this could be addressed in personalized treatment and relapse prevention (Bulik, 2016). Sex-specific genetic and biological factors may partially underlie increased risk for AN in females which suggests that new and focused studies of body composition and metabolism in AN patients could increase our understanding of AN etiology and response to treatment.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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5 Genetic correlations of psychiatric traits with body composition and glycemic traits are sex- and age-dependent

This chapter, investigating sex differences in genetic correlations of body composition, metabolic and psychiatric traits across 17 psychiatric traits, is presented as a manuscript of an accepted paper. It is an exact copy of this manuscript.

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Supplementary materials for this chapter, as detailed in the text, are attached in **Appendix 5** and in the folder **Chapter 5** on the CD.

Full author lists for each consortium are available in **Appendix 6**.

Genetic correlations of psychiatric traits with body composition and glycemic traits are sex- and age-dependent

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Keywords: fat-free mass, body fat percentage, physical activity, insulin, ADHD, anorexia nervosa, schizophrenia, OCD

5.1 Abstract

Body composition is often altered in psychiatric disorders. Using genomewide common genetic variation data, we calculate sex-specific genetic correlations amongst body fat %, fat mass, fat-free mass, physical activity, glycemic traits and 17 psychiatric traits (up to N = 217,568). Two patterns emerge: (1) anorexia nervosa, schizophrenia, obsessive-compulsive disorder, and education years are negatively genetically correlated with body fat % and fat-free mass, whereas (2) attention-deficit/hyperactivity disorder (ADHD), alcohol dependence, insomnia, and heavy smoking are positively correlated. Anorexia nervosa shows a stronger genetic correlation with body fat % in females, whereas education years is more strongly correlated with fat mass in males. Education years and ADHD show genetic overlap with childhood obesity. Mendelian randomization identifies schizophrenia, anorexia nervosa, and higher education as causal for decreased fat mass, with higher body fat % possibly being a causal risk factor for ADHD and heavy smoking. These results suggest new possibilities for targeted preventive strategies.

5.2 Introduction

Psychiatric disorders are complex traits influenced by thousands of genetic variants that act in concert with environmental factors[1,2]. Genome-wide association studies (GWASs) of psychiatric disorders have identified more than 300 independent genomic loci[3,4], informed biological follow-up studies[5], and may deliver promising targets for drug discovery and repurposing[6–8]. Genomewide summary statistics generated by GWAS can be used in several different ways[9] including estimating single nucleotide polymorphism-based heritability (h^2_{SNP}), which is the phenotypic variance explained by common genomic variants. Values of h^2_{SNP} range from 10 to 30% for psychiatric disorders and typically capture around a third of the heritability estimated by twin studies[10]. Additionally, genetic correlations can be calculated using GWAS summary statistics via bivariate linkage disequilibrium score regression (LDSC), which estimates the genetic overlap (i.e., the shared genetic effects) between two traits[11,12]. Such GWAS based genetic correlation analyses have shown substantial genetic overlap among psychiatric disorders[13], providing evidence for an underlying "p factor" representing general liability for psychiatric illness[14,15]. For instance, genomic structural equation modelling[16] of GWAS summary statistics for schizophrenia, bipolar disorder, major depressive disorder, post-traumatic stress disorder, and anxiety showed that they load onto one shared latent factor with loading estimates between 0.29-0.86[16]. However, marked differences in the clinical presentation of psychiatric disorders exist for psychotic experiences or dysfunctional reward systems, suggesting the existence of additional disorder-specific genetic effects[13,14,16].

Clinically, many psychiatric disorders are accompanied by disturbances in appetite regulation, eating behaviour, and altered physical activity. These disturbances can alter body composition and result in comorbid overweight or underweight[17], most prominently observed in eating disorders, such as binge-eating disorder and anorexia nervosa[18]. Such severe weight dysregulation typically reduces patients' quality of life and is associated with excess morbidity and mortality[19]. Body composition traits, including body fat % and fat-free mass, are also complex, with substantial twin heritabilities of about 70%[20,21]. BMI is the most commonly studied body composition phenotype and its associated genetic variants have been found

to be significantly overrepresented in genes and genomic regions active in brain cell types[22], suggesting it may be a partially behavioural trait. Several studies have also shown negative genetic correlations of BMI with anorexia nervosa and schizophrenia[12,23–25] and positive genetic correlations of BMI with ADHD and major depressive disorder[26,27]. These observations suggest that an in-depth investigation of the shared genomics between psychiatric and body composition traits is needed.

In addition, both extreme overweight and extreme underweight show a clear sex difference: females are not only disproportionately affected by anorexia nervosa (with ratios up to 15:1), but also by obesity (≥ 30 kg/m^2)[28–30]. Sex differences are not limited to body composition: major depressive disorder[31] and anxiety[32] are more common in females, whereas attention-deficit/hyperactivity disorder (ADHD)[33] and autism spectrum disorder[34] occur more often in males. Sex differences in body composition, psychiatry, and their interplay are not fully understood. Hormones and sex chromosomes have clearly been demonstrated to play a role[35], but are insufficient to fully explain the sex differences[36].

In this study, our primary aim is to identify pairs of traits with shared genetic factors by calculating sex-specific genetic correlations. To do so, we calculate sex-specific genetic correlations for GWASs of 12 psychiatric disorders mostly supplied by the Psychiatric Genomics Consortium (URLs) and five behavioural traits with sex-specific GWAS of body composition traits derived from a healthy and medication-free subsample of the UK Biobank (URLs; Supplementary Tables 1 & 2). These include BMI, body fat % (BF%), absolute fat mass (FM), and fat-free mass (FFM) as well as body composition-related traits, such as objectively-measured physical activity from the UK Biobank (URLs) and glycemic traits from MAGIC (URLs; Supplementary Data 1). We apply trait-specific illness- and medication filtering to obtain genomic variants that are associated with body composition traits independent of the confounding effects of somatic diseases, such as diabetes or endocrine illnesses, addiction-related behaviors, including smoking and alcohol consumption, as well as psychiatric disorders. Where possible, putative causality is examined using generalized summary data-based Mendelian randomization

(GSMR)[37] in females and males separately. As a secondary aim, we use GWAS of BMI and fat-free mass from different stages of life, including childhood, adolescence, young adulthood, and late adulthood, to identify the developmental stages in which the sharing of body composition genomic factors with genetic risk for psychiatric disorders occurs.

Here, we show that the genomic overlap between body composition traits and psychiatric disorders is evident only in later adulthood, whereas childhood and young adulthood GWAS of body mass index do not correlate significantly with psychiatric traits. Accelerometer-measured physical activity shows genetic correlations with obsessive-compulsive disorder and anorexia nervosa, but with no other psychiatric disorder. In addition, glycaemic traits show significant genetic correlations only with anorexia nervosa and years of education, which positions anorexia nervosa as unique amongst the psychiatric disorders we investigate. These findings encourage a deeper investigation of metabolic pathways that may be implicated in psychiatric disorders to identify potential targets for preventive strategies.

5.3 Results

Genetic overlap between the sexes. Body composition and physical activity showed substantial heritability explained by common genetic variation ranging from 28-51% (standard error (se) = 0.4-0.8%, LDSC; Supplementary Table 3) and sex-dependent sets of genomic variation at $p_{\text{Bonferroni}} = 0.05/28 = 0.002$. We detected a genetic correlation between males and females in body fat % that was significantly different from 1 ($r_g = 0.89$, se = 0.03; $p_{\neq 1} = 4.7 \times 10^{-4}$, LDSC). Sensitivity analyses using Haseman-Elston regression[38] confirmed these results (Supplementary Table 3) and suggest that specific sets of genomic variation associated with body fat % may be differentially active in females and males. The genetic correlations between females and males for the remaining traits are presented in Supplementary Table 4. Detailed results for the body composition and physical activity GWASs, including significant hits and Manhattan plots, are presented on Functional Mapping and Annotation (FUMA; URLs) entry 20-22 and 38-41.

Genetic overlap of psychiatric and body composition traits. In the genetic correlations of the psychiatric disorders and behavioral traits with body composition and physical activity, distinct patterns emerged resulting in two groups (Table 1). In the first group anorexia nervosa, education years, obsessive-compulsive disorder (OCD), and schizophrenia were significantly negatively associated with body fat % while anorexia nervosa and schizophrenia were also significantly negatively associated with fat-free mass (see Fig. 1 and Supplementary Data 2 for full results). By contrast, in the second group, ADHD, heavy smoking, alcohol dependence, and insomnia were significantly positively associated with body fat % while only ADHD and heavy smoking were also significantly positively associated with fat-free mass (Table 1). The *p* value threshold for the genetic correlations with body composition traits was $p_{\text{Bonferroni}} = 0.05/190 = 2.6 \times 10^{-4}$ using matrix decomposition of the genetic correlation matrix to identify the number of independent tests to adjust the threshold using Bonferroni correction[39].

Table 1. Significant genetic correlations between psychiatric disorders, behavioral traits and body composition traits.

Psychiatric/behavioral trait	Body composition	r_g	se	*p*
Group 1				
Anorexia nervosa	Body fat %	-0.34	0.03	2.09×10^{-27}
Anorexia nervosa	Fat-free mass	-0.14	0.03	5.79×10^{-6}
Education years	Body fat %	-0.34	0.02	7.11×10^{-60}
Education years	Fat-free mass	-0.03	0.02	0.14 (n.s.)
OCD	Body fat %	-0.31	0.05	9.82×10^{-10}
OCD	Fat-free mass	-0.12	0.04	0.01 (n.s.)
Schizophrenia	Body fat %	-0.09	0.02	7.30×10^{-6}
Schizophrenia	Fat-free mass	-0.08	0.02	2.00×10^{-4}
Group 2				
ADHD	Body fat %	0.30	0.03	2.50×10^{-21}
ADHD	Fat-free mass	0.17	0.03	3.84×10^{-11}
Smoking	Body fat %	0.29	0.03	3.59×10^{-23}
Smoking	Fat-free mass	0.15	0.03	9.94×10^{-8}
Alcohol dependence	Body fat %	0.23	0.06	2.00×10^{-0}
Alcohol dependence	Fat-free mass	0.04	0.05	0.45 (n.s.)
Insomnia	Body fat %	0.23	0.04	2.27×10^{-8}
Insomnia	Fat-free mass	0.06	0.03	0.11 (n.s.)

Note. The correlations were calculated using linkage disequilibrium score regression (LDSC, Bulik-Sullivan et. al, 2015). The table presents the significant findings. The full results can be found in Supplementary Data 2. Bonferroni-corrected *p* value threshold: $a = 0.05/190 = 0.0002$.

Abbreviations: r_g = genetic correlation; se = standard error; *p* = p value; n.s. = not significant after correction for multiple testing; ADHD = attention-deficit/hyperactivity disorder, OCD = obsessive-compulsive disorder

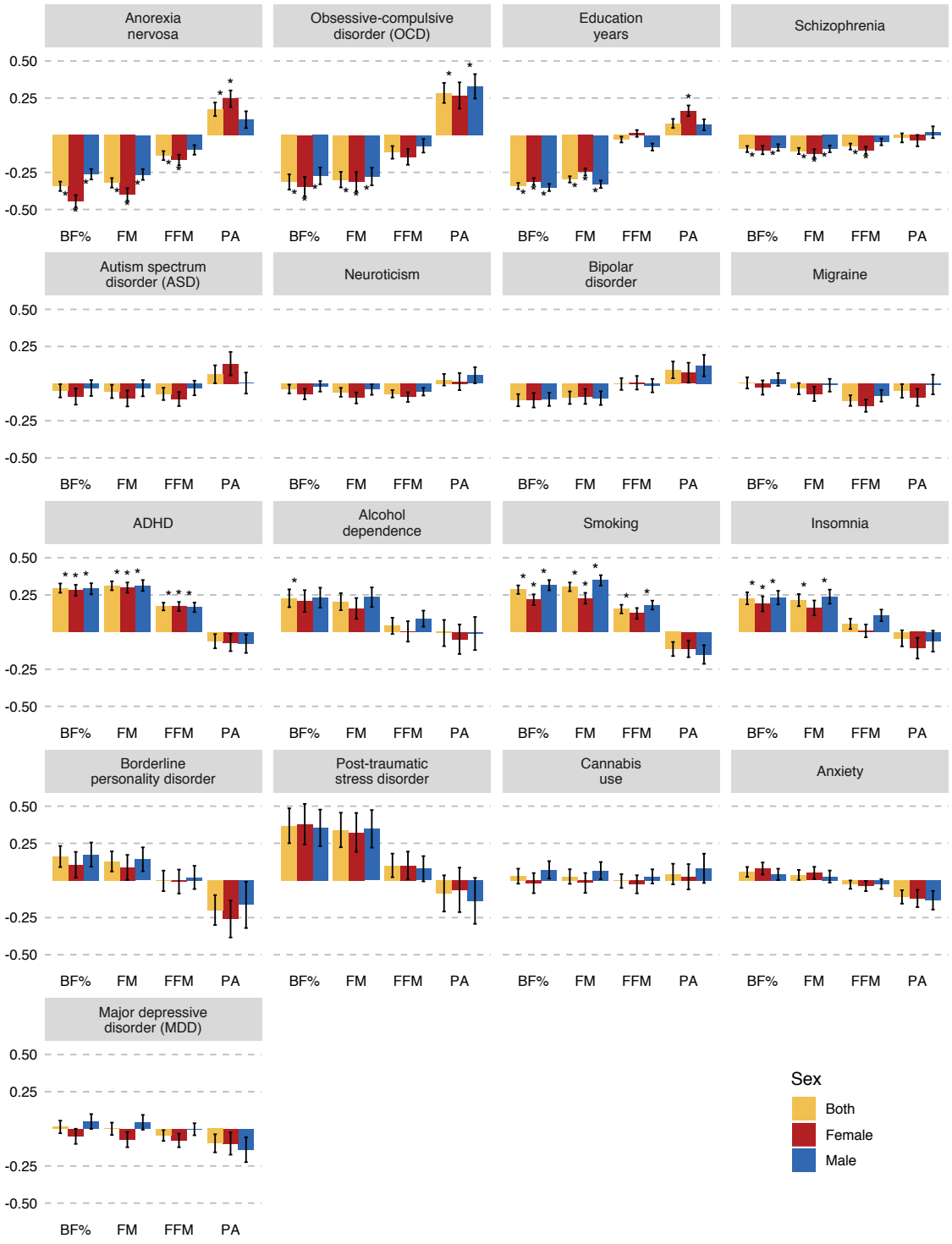

Fig. 1 Sex-specific genetic correlations across body composition, physical activity, and psychiatric traits.

Sex-specific genetic correlations of body composition traits (*n* = up to 155,961) and physical activity (*n* = up to 66,224) with sex-combined psychiatric disorders (*n* = up to 77,096) and behavioral traits (*n* = up to 157,355). The autosomal genetic correlations were calculated by bivariate linkage disequilibrium score regression

(LDSC). Colored bars represent genetic correlations, error bars depict standard errors (SE) and asterisks indicate statistically significant genetic correlations with p values less than α = 0.0003. This threshold was calculated via the identification of the number of independent tests using matrix decomposition of the genetic correlation matrix and subsequent Bonferroni correction of α = 0.05 for 190 independent tests. ADHD = attention-deficit/hyperactivity disorder, BF% = body fat percentage, FFM = fat-free mass, FM = fat mass, PA = physical activity

Sex differences in genetic correlations. The genetic correlation of anorexia nervosa with body fat % in females (r_g = -0.44, se = 0.04, LDSC) was stronger than with body fat % in males (r_g = -0.26, se = 0.04, LDSC) with a significant difference of δr_g= -0.17 (p = 4.2 x 10^{-5}, LDSC jackknife). Conversely, education years showed a stronger genetic correlation with fat mass in males than in females (δr_g= 0.10, p = 1.3 x 10^{-4}, LDSC jackknife) which was also seen with fat-free mass (δr_g = 0.09, p = 1.7 x 10^{-4}, LDSC jackknife). No other sex differences were observed (Supplementary Data 3).

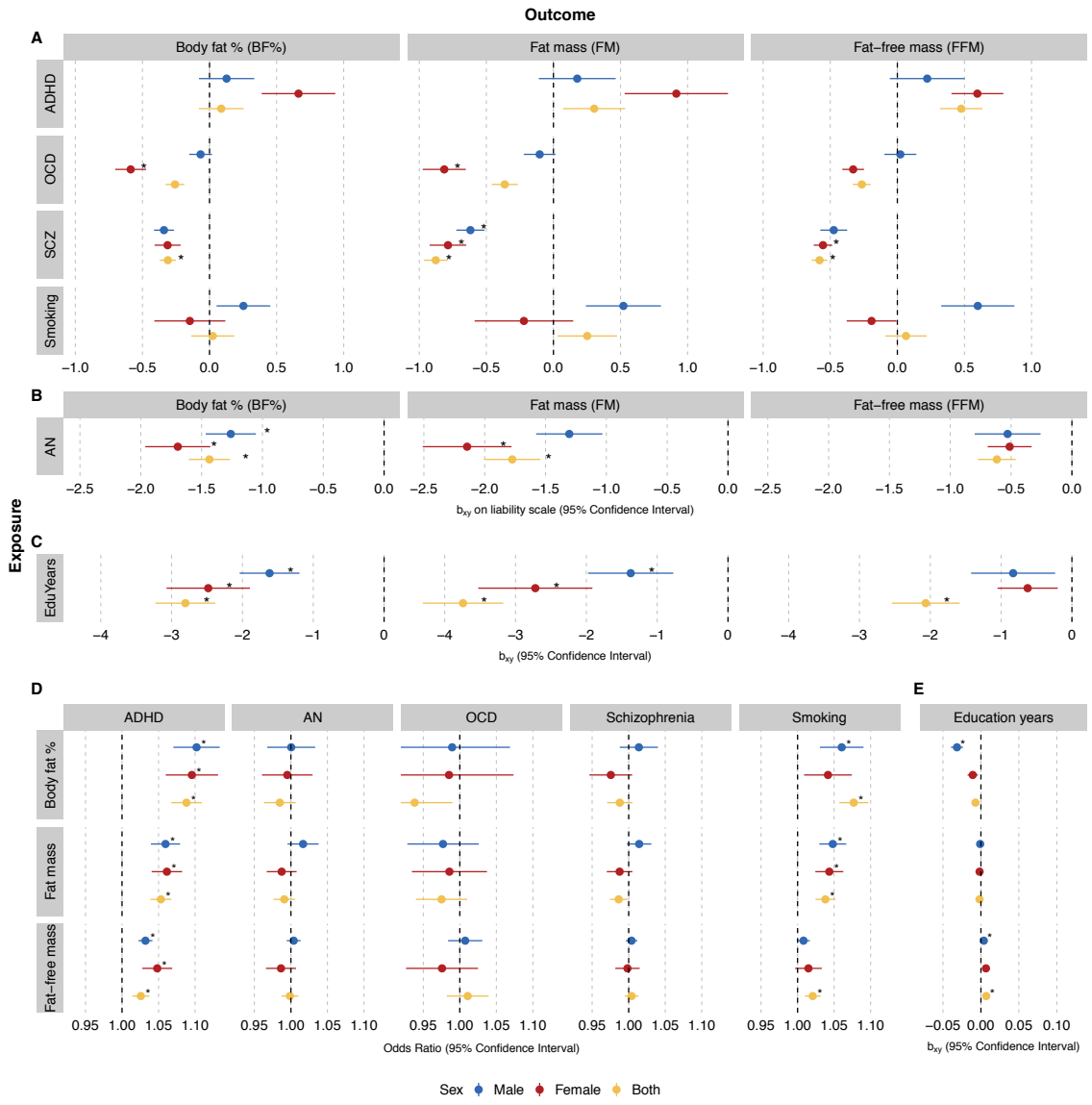

Fig. 2 Causal associations between body composition and psychiatric traits. Results are shown from generalized summary data-based Mendelian randomization (GSMR) analyses. Colors represent the sex of the body composition trait: red for female effects, blue for male effects, and yellow for sex-combined effects. Error bars represent 95% confidence intervals (95% CIs) and asterisks indicate statistically significant estimates with *p* values less than $\alpha = 2.6 \times 10^{-4}$.

Panel A: Putative causal associations of exposures (rows) psychiatric disorders (*n* = up to 77,096) and behavioral traits (*n* = up to 217,568) with outcomes (columns) body composition traits (*n* = up to 155,961). Dots represent the effect sizes (as measured by betas, b_{xy}) on the liability scale of the disorders or traits.

Panel B & C: Mendelian randomization results for the exposures anorexia nervosa and education years on the outcomes the body composition traits. These are plotted

differently due to the size of the effects. All estimates are presented together in Supplementary Fig. 1 on the same scale.

Panel D: Putative causal associations of exposures (rows) body composition traits (*n* = up to 155,961) with outcomes (columns) psychiatric disorders (*n* = up to 77,096) and behavioral traits (*n* = up to 217,568). Dots represent the effect sizes (as measured by odds ratios, ORs) of risk factors on disorders or traits.

Panel E: The Mendelian randomization results for body composition traits as exposures on the outcome years of education. Dots represent the effect sizes (as measured by betas, b_{xy}) on the scale of the risk factors.

Abbreviations. ADHD = attention-deficit/hyperactivity disorder, AN = anorexia nervosa, BF% = body fat percentage, EduYears = education years, FFM = fat-free mass, FM = fat mass, OCD = obsessive compulsive disorder, SCZ = schizophrenia

Putative causal relationships. Generalized summary data-based Mendelian randomization (GSMR) revealed evidence consistent with putative causal relationships between psychiatric traits and body composition. The effects on continuous traits are expressed as beta coefficients (β; Fig. 2A, B, C, & E, Supplementary Fig. 1), whereas the effects on binary traits are presented as odds ratios (OR; Fig. 2D). Estimates with binary exposures were converted to the liability scale[40]. The Bonferroni-corrected *p* value was 0.05/190 = 2.6×10^{-4} for the GSMR analyses (Supplementary Data 4-5). In the first group, GSMR showed evidence for a 1.8 kg decrease in fat mass per standard deviation of liability to anorexia nervosa ($p = 2.3 \times 10^{-8}$, GSMR) that was more pronounced in females ($\beta_{AN \rightarrow FM} = -2.14$, $p = 1.9 \times 10^{-5}$, GSMR) than in males ($\beta_{AN \rightarrow FM} = -1.3$, $p = 4.9 \times 10^{-4}$, GSMR). This mirrored the observed genetic correlations. Additionally, GSMR showed evidence for a 3.7 kg decrease in fat mass per year of education ($p = 5.0 \times 10^{-38}$, GSMR). Furthermore, GSMR showed a 0.88 kg decrease in fat mass ($p = 3.3 \times 10^{-13}$, GSMR) and a 0.58 kg decrease in fat-free mass ($p = 4.5 \times 10^{-13}$, GSMR) per standard deviation of liability to schizophrenia (Supplementary Data 4). GSMR results for the second group showed no evidence for an influence of ADHD on body fat % ($p = 0.64$, GSMR). However, GSMR showed evidence in the reverse direction with a 1.05-fold increase in risk for ADHD per kg fat mass ($p = 1.3 \times 10^{-12}$, GSMR) as well as a 1.03-fold increase in risk for ADHD per kg fat-free mass ($p = 2.0 \times 10^{-5}$,

GSMR) and a 1.04-fold increase in heavy smoking per kg fat mass (p = 6.7 x 10^{-8}, GSMR; Supplementary Data 5**)**.

Genetic correlations with physical activity. In the first group, OCD (r_g = 0.28, se = 0.07, LDSC) and anorexia nervosa (r_g = 0.25, se = 0.06, LDSC) correlated positively with objectively-measured physical activity, whereas education years showed a significant correlation with physical activity only in females (r_g = 0.17, se = 0.04, LDSC; Supplementary Data 2). However, when formally tested the genetic correlation was not significantly different from the correlation observed in males (Supplementary Data 3). Neither ADHD (p = 0.20, LDSC) nor any other trait in the second group correlated with physical activity (Supplementary Data 2).

Fig. 3 Sex-specific genetic correlations across glycemic traits and psychiatric traits.

Sex-specific genetic correlations of glycemic traits (n = up to 140,583) with sex-combined psychiatric disorders (n = up to 77,096) and behavioral traits (n = up to 157,355). The autosomal genetic correlations were calculated by bivariate linkage disequilibrium score regression (LDSC). Colored bars represent genetic

correlations, error bars depict standard errors (SE) and asterisks indicate statistically significant genetic correlations with p values less than $\alpha = 0.0002$. This threshold was calculated via the identification of the number of independent tests using matrix decomposition of the genetic correlation matrix and subsequent Bonferroni correction of $\alpha = 0.05$ for 231 independent tests. ADHD = attention-deficit/hyperactivity disorder, Glu = fasting glucose, Ins = fasting insulin, IR = insulin resistance, adj = adjusted

Genetic correlations with glycemic traits. Our investigation into whether the relationships of the psychiatric traits with body composition are mirrored in their relationships with the glycemic traits (Fig. 3) showed that anorexia nervosa (r_g = -0.28; $p = 1.8 \times 10^{-7}$, LDSC) and education years (r_g = -0.28, $p = 1.0 \times 10^{-12}$, LDSC) correlated genetically negatively with fasting insulin concentrations. Accordingly, anorexia nervosa (r_g = -0.29, $p = 2.8 \times 10^{-5}$, LDSC) and education years (r_g = -0.33, $p = 9.2 \times 10^{-6}$, LDSC) showed also negative genetic correlations with insulin resistance. In addition, education years showed a negative genetic correlation with fasting glucose concentrations (r_g = -0.14; $p = 2.1 \times 10^{-5}$, LDSC) whereas heavy smoking showed a positive genetic correlation with fasting glucose concentrations (r_g = 0.22; $p = 2.0 \times 10^{-4}$, LDSC; Supplementary Data 6). No other psychiatric traits showed a genetic correlation with glycemic traits passing our significance threshold.

Sensitivity analyses with female-only and male-only GWAS of the psychiatric and behavioural traits resulted in similar results, indicating that the patterns and results are consistent and largely independent of female to male ratios in the sex-combined GWAS (Supplementary Data 2, 6 & Supplementary Fig. 2a-3b). Sensitivity analyses not adjusting the body composition GWAS for alcohol consumption or smoking yielded the same results (Supplementary Data 7).

Age-dependent genetic correlations. As a secondary aim, we explored the developmental dependence of genetic correlations of BMI and fat-free mass at different ages with psychiatric disorders and behavioural traits (Fig. 4). We used BMI as a proxy measure of body fat % as no GWAS of body fat % in childhood or

adolescence were available. To test if the sets of genetic variants affecting body composition at different stages of life differentially correlate with psychiatric disorders and behavioural traits, we estimated the following genetic BMI correlations and tested if they were significantly different from one[41]: between childhood and adolescence/young adulthood (r_g = 1.00, se = 0.07, LDSC), between childhood and later adulthood (r_g = 0.66, se = 0.04, LDSC), and adolescence and later adulthood (r_g = 0.80, se = 0.05, LDSC). The genetic correlation of fat-free mass between childhood and adulthood was also significantly different from one (r_g = 0.30, se = 0.04, LDSC). As above, multiple psychiatric disorders and traits showed significant positive and negative genetic correlations with adult BMI and fat-free mass. However, BMI in childhood, adolescence, or young adulthood, nor fat-free mass in childhood, showed significant genetic correlations with any of the psychiatric disorders or behavioural traits (Supplementary Data 8). To additionally test an extreme phenotype, we calculated genetic correlations between psychiatric traits and obesity in childhood. Within the first group, only education years (r_g = -0.19, se = 0.03, LDSC) correlated negatively with obesity in childhood. In the second group, ADHD in males was the only psychiatric disorder that showed a significant positive genetic correlation with obesity in childhood (r_g = 0.26, se = 0.05, LDSC). GSMR analyses gave evidence for a 1.42-fold increase for ADHD per kg/m^2 increase in childhood BMI (p = 1.26 x 10^{-8}, GSMR).

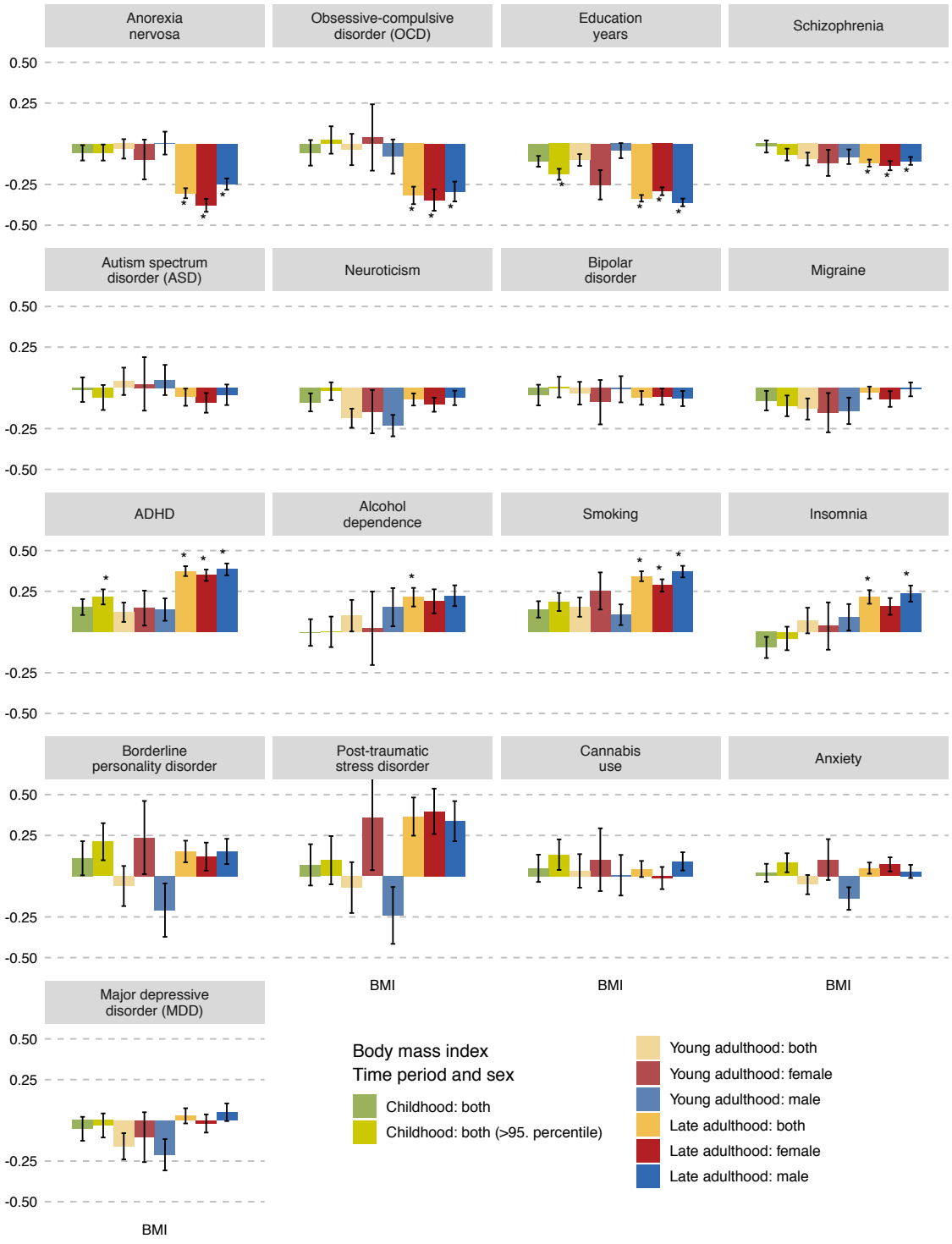

Fig. 4 Age-dependence of sex-specific genetic correlations across body composition and psychiatric traits.

Sex-specific genetic correlations of body mass index (BMI) and fat-free mass (n = up to 157,355) with psychiatric disorders (n = up to 77,096) and behavioral traits (n = up to 157,355) across the lifespan. Participants of the childhood BMI GWAS (green, n = 35,668) were younger than 10 years, the participants of the young adulthood GWASs

(lighter colors, n = 29,054) were between 15-35 years, participants of the late adulthood GWAS (darker colors, n = 155,961) were between 39-75 years old. Overweight in childhood (lime green; n = 13,848) was included as an extreme phenotype. The autosomal genetic correlations were calculated by bivariate linkage disequilibrium score regression (LDSC). Colored bars represent genetic correlations, error bars depict standard errors (SE) and asterisks indicate statistically significant genetic correlations with p values less than α = 0.0002. This threshold was calculated via the identification of the number of independent tests using matrix decomposition of the genetic correlation matrix and subsequent Bonferroni correction of α = 0.05 for 210 independent tests. ADHD = attention-deficit/hyperactivity disorder

5.4 Discussion

Symptomatically, psychiatric disorders are often accompanied by alterations in energy intake, energy expenditure, and body composition. Recent genetic analyses of BMI found an important role for genes expressed in the brain and specific brain cell types[22], suggesting that BMI may be a metabo-behavioural trait. This spurred our in-depth investigation of the shared genetics of psychiatric traits and body composition. We were able to show that five psychiatric disorders––anorexia nervosa, OCD, schizophrenia, ADHD, and alcohol dependence––as well as three behavioural traits––education years, insomnia, and heavy smoking––show significant genetic correlations (i.e., shared genetics) with body composition in two distinct patterns.

The first group of psychiatric disorders and behavioural traits included anorexia nervosa, OCD, schizophrenia, and education years and was characterized by genetic correlations with genomic variants predisposing to lower body fat % and fat-free mass. The second group comprised ADHD, alcohol dependence, heavy smoking, and insomnia and had genetic correlations with genomic variants predisposing to higher body fat % and fat-free mass. Our Mendelian randomization analyses, used significant genetic variants as instrumental variables and found that anorexia nervosa, schizophrenia, and education years showed evidence consistent with a negative causal effect on body fat % and, in the reverse direction, higher body fat % appeared to be a risk factor for both ADHD and heavy smoking. Our results also suggested that the overweight seen in individuals with schizophrenia

in epidemiological studies[42] is likely to represent medication effects[43] given our observations of a putative causal effect of schizophrenia on lower fat mass and fat-free mass. This finding reiterates the pressing need for the development of new antipsychotic medications with more favorable weight-related side effect profiles. In our analysis, anorexia nervosa showed a stronger correlation with body fat % in females than in males. This phenomenon was not observed for other traits genetically associated with anorexia nervosa, such as neuroticism, anxiety, major depressive disorder, OCD, or schizophrenia[41]. These findings suggest that anorexia nervosa and body fat % may share a sex-dependent set of genomic variants potentially contributing to its marked sex bias in its prevalence. Education years showed a stronger genetic correlation with fat mass in males than in females. However, the GSMR analysis showed a more pronounced protective effect of education years on fat mass in females than in males in line with a large epidemiological study[44]. This suggests that the stronger genetic association between education years and fat mass in males may be driven by a set of pleiotropic variants.

From a developmental perspective, it is striking that GWAS of body composition across ages do not genetically correlate perfectly with each other. These varying genetic effects across the lifespan[41,45] have been termed "genetic innovation"[46] and represent the effects of partially different, age-dependent sets of genomic variants on body composition regulation at certain periods of life[41,45]. Some of the psychiatric disorders, such as ADHD and anorexia nervosa, typically have their onset in childhood or adolescence with preceding symptoms or behaviors that implicate neurodevelopmental components. We used the available life-stage GWAS of body composition and did not find genetic overlap between childhood or adolescence/young adulthood BMI with psychiatric disorders, but instead found significant genetic correlations of psychiatric disorders with later adult BMI and body fat %. Our analyses also show that genetic variants associated with obesity before the age of ten were positively correlated only with ADHD and negatively only with education years. The relatively specific positive genetic correlation of childhood obesity with ADHD recapitulates a large body of clinical evidence of high

phenotypic comorbidity[47], also shown in family studies[48]. Overweight may represent a difficult but potentially intervenable risk factor at a young age. Our finding of a genetic overlap between ADHD and obesity in childhood may implicate shared biological pathways between both traits. Given our other results, it appears that this shared component is unlikely to be related to physical activity or glycemic traits. Instead, speculatively, a central nervous system pathway that is dysregulated by increased body mass in childhood may increase the liability to develop ADHD.

We also investigated body composition-related traits including physical activity, fasting insulin and fasting glucose concentrations. Physical activity showed a positive genetic correlation with anorexia nervosa and OCD, which themselves were negatively genetically correlated with body fat %. Carrying genetic variants that predispose to higher physical activity may be associated with the relationship between lower body fat % and psychiatric traits. Higher physical activity, therefore, should be carefully assessed in the treatment of patients with compulsive psychiatric disorders like anorexia nervosa and OCD as it may be a genetically mediated behaviour, as indicated by our analysis.

Contrary to our expectations, ADHD did not show a genetic correlation with physical activity. This suggests that hyperactivity in ADHD may not originate from biological liability for higher accelerometer-measured physical activity[49] and is likely to have an alternative cause, such as insufficient inhibitory control as observed in pediatric clinical samples with ADHD[50], healthy adult population samples[51], and in a large longitudinal developmental cohort study[52].

Our analyses showed that anorexia nervosa and education years have a negative genetic correlation with fasting insulin concentrations and insulin resistance, positioning anorexia nervosa as a special case within the psychiatric disorders and potentially differentiating it from OCD. These negative correlations with fasting insulin concentrations mirrored the negative genetic correlations between anorexia nervosa, education years, and body fat %. The involvement of metabolic hormones like insulin in anorexia nervosa underscores the relationship of brain

and body and their reciprocal regulation[53], opening an avenue for deeper investigation of metabolic components in psychiatric disorders. The genetic correlations of ADHD with glycemic traits were not significant, implying that these traits play a smaller role in ADHD than in anorexia nervosa, given the comparable sample size of the GWAS on both psychiatric disorders[25,26]. Genetic associations of physical activity and glycemic traits with body composition and psychiatric traits in plausible directions render them interesting candidates for formal mediation analyses as they may be actionable targets[54].

Our study represents the largest investigation of sex- and age-dependent effects in the genomic overlap of body composition and psychiatric traits. Although our analyses drew on the largest available GWASs, some phenotypes still had relatively small sample sizes for genomic investigations of common variants in complex traits, especially for our sex-specific analyses. These should be repeated when sample sizes have increased, especially for OCD as its currently available GWAS sample size is particularly modest. All Mendelian randomization analyses, using GSMR[37], with body composition or glycemic traits, ADHD, education years, schizophrenia, or heavy smoking as exposure were sufficiently powered; however, the analyses with anorexia nervosa, insomnia, or OCD as exposures should be regarded as exploratory in nature because *p* value thresholds were lowered to include at least 10 SNPs in the instrument variable.

Finally, the age-dependent genetic influences we observed between psychiatric traits and body composition suggests future research could focus on a developmental approach to GWAS analyses of body composition, to capture age- and sex-dependent differences. These differences have already been suggested by larger twin studies[55,56] and two molecular genetic studies[41,45] which enabled our examination of their relationship with psychiatric traits. Most importantly, shared biological pathways and common environmental factors influencing both body composition and behavioural traits should be studied as potential targets for interventions.

5.5 Methods

UK Biobank subsample. We performed genome-wide association studies (GWAS) on an unrelated (KING relatedness metric >0.044, equivalent to a relatedness value of 0.088; $n_{related}$ = 7,765) European subsample (defined by *4*-means clustering of the genetic principal components)[57] of the genotyped UK Biobank participants (*n* = 155,961, 45% female, 32% of the genotyped participants, Supplementary Table 1)[58,59]. The UK Biobank (URLs) is a prospective cohort sampled from the general population between 2006-2010. All participants were between 40 to 69 years old, were registered with a general practitioner through the United Kingdom's National Health Service, and lived within traveling distance of one of the assessment centres.

Ethics. The UK Biobank is approved by the North West Multi-centre Research Ethics Committee. All procedures performed in studies involving human participants were in accordance with the ethical standards of the North West Multi-centre Research Ethics Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All participants provided written informed consent to participate in the study. This study has been completed under UK Biobank approved study application 27546.

Power calculations of the GWASs. We conducted power calculations for the female and male GWAS using the Genetic Power Calculator[60]. A minimum of 39,580 individuals is required to detect a SNP that accounts for 0.1% of trait variance at 80% power at a genome-wide significance threshold of $p \leq 5x10^{-8}$ and a MAF 0.20. According to these results the female and the male GWAS were sufficiently powered to detect genome-wide significant loci with 70,700 females and 85,261 males. With these parameters, the female GWAS had a power of 99.8% and the male GWAS of 99.9%.

GWAS on body composition traits in the UK Biobank. The continuous body composition traits––body fat %, fat mass, fat-free mass, and BMI––were measured using the validated bioelectrical impedance analyzer Tanita BC-418 MA (Tanita Corporation, Arlington Height, IL) at every assessment centre[61,62] for every

participant across the UK. We applied trait-specific medication and illness filtering to exclude participants with compromised hydration status and medications or illnesses known to affect body composition to identify genetic variation association with body composition phenotypes that are not confounded by illnesses and their downstream effects or metabolism-changing medication. We applied stringent exclusion criteria and covaried for addictive behaviour-related phenotypes, including smoking and alcohol consumption (for exclusion criteria, see Supplementary Table 2). We regressed the body composition traits on factors related to assessment centre, genotyping batch, smoking status, alcohol consumption, menopause, and continuous measures of age, and socioeconomic status (SES) measured by the Townsend Deprivation Index[63] as independent variables. We took the residuals from these regressions as our phenotypes for the GWAS. We included 7,794,483 single nucleotide polymorphisms and insertion-deletion variants (hereafter referred to as SNPs) with a minor allele frequency >1%, imputation quality scores >0.8, and that were genotyped, or present in the HRC reference panel[64] and used an additive model on the imputed dosage data provided by UK Biobank, using BGENIE v1.2[65]. We accounted for underlying population stratification by including the first six principal components, calculated on the genotypes of our European subsample using FlashPCA2[66]. We performed GWAS including incremental numbers of principal components and checked each GWAS for inflation by calculating its LDSC intercept. We identified six principal components as the optimal number to adjust for population stratification within the European subsample and to not overcorrect the analysis retaining the greatest signal. Additionally, we included assessment centre as a covariate to adjust for population stratification.We then meta-analyzed the sex-specific GWAS using METAL[67] (URLs) applying an inverse variance-weighted model with a fixed effect, to obtain sex-combined results.

Clumping and genome-wide significant loci. Significantly associated SNPs ($p < 5x10^{-8}$) were considered as potential index SNPs. SNPs in LD ($r^2 > 0.2$) with a more strongly associated SNP within 3000 kb were assigned to the same locus using Functional Mapping and Annotation (FUMA, URLs)[68]. Overlapping clumps were merged with a second clumping procedure in FUMA, merging all lead SNPs

with r^2 = 0.1 to genomic loci. After clumping, independent genome-wide significant loci ($5x10^{-8}$) were compared with entries in the NHGRI-EBI GWAS catalog[69], using FUMA[68].

Heritability estimation and investigation of sex differences. To ensure the robustness of our results, we applied multiple approaches to calculate heritability estimates and genetic correlations. We used BOLT-LMM[70], LDSC[11], and GREML[71] implemented in GCTA[72] to calculate common variant h^2_{SNP} (URLs). Additionally, we calculated the genetic correlation between females and males using LDSC[11] and Haseman-Elston regression[38] implemented in GCTA[72] to estimate sex differences in the genetic architecture of the body composition, glycemic traits, and physical activity. Haseman-Elston regression uses the cross product of phenotypes for pairwise individuals and a genetic relatedness matrix to calculate heritability and genetic correlations[73]. All other statistics were calculated in R 3.4.1 if not otherwise stated (URLs).

GWAS of psychiatric disorders and behavioral traits. All of the following traits were used for the sex-specific and age-dependent analyses (Supplementary Data 1). The sex-specific summary statistics for the psychiatric disorders, including major depressive disorder[27], schizophrenia[3], anorexia nervosa[25], bipolar disorder[74,75], ADHD[26,76], alcohol dependence[77], autism spectrum disorder[78], and PTSD[79] were provided by the PGC (URLs), for obsessive-compulsive disorder[80,81] by International Obsessive Compulsive Disorder Foundation Genetics Collaborative (IOCDF-GC) and OCD Collaborative Genetics Association Studies (OCGAS), for borderline personality disorder[82] by the German Borderline Genomics Consortium, for cannabis use by the International Cannabis Consortium[83], for anxiety[84] by our own group, for insomnia[85] by the Complex Trait Genetics at VU University Amsterdam (URLs), for heavy smoking[86] by University of Leicester available from the UK Biobank (URLs), for the behavioural traits years of education[87] by the Social Science Genetic Association Consortium (URLs), for neuroticism[41] by our own group (Supplementary Data 1) and for migraine[88,89] by International Headache Genetics Consortium (IHGC). Glycemic traits[90] summary statistics were provided by the Meta-Analyses of Glucose and Insulin-related traits

Consortium (MAGIC), whereas childhood obesity[91] results were provided by the Early Growth Genetics (EGG, URLs) Consortium, BMI in young adulthood by Graff et al.[92] and physical activity by our group[41].

Genetic correlations. Using an analytic extension of LDSC[11], we calculated SNP-based bivariate genetic correlations (r_g) to examine the genetic overlap of body composition and glycemic traits with psychiatric and behavioural traits and disorders in a sex-specific manner. Differences in genetic correlations were calculated and their standard errors were calculated using a block jackknife approach as previously described[41].

Generalized summary data-based Mendelian randomization. We investigated putative causal bidirectional relationships between these traits using generalized summary data-based Mendelian randomization (GSMR)[37]. Mendelian randomization is a method that uses genetic variants as instrumental variables, which are expected to be independent of confounding factors, to test for causative associations between an exposure and an outcome[93]. Mendelian randomization can be used to infer credible causal associations when randomized-controlled trials are not feasible or are unethical[93]. GSMR performs a multi-SNP Mendelian randomization analysis using summary statistics. Let *z* be a genetic variant (e.g., SNP), *x* be the exposure (e.g., psychiatric disorder) and *y* be the outcome (e.g., body composition trait). The basic idea of GSMR is that, if there are multiple independent (or nearly independent) SNPs (*z*) associated with *x* and the effect of *x* on *y* is causal, then all the *x*-associated SNPs will have an effect on *y* through *x*. In this case, b_{xy} at any of the *x*-associated SNPs is expected to be identical in the absence of pleiotropy as all the SNP effects on *y* are mediated by *x*. Therefore, increased statistical power can be achieved by integrating the estimates of b_{xy} from all the *x*-associated SNPs using a generalized least squares (GLS) approach[37,94]. The GSMR method essentially implements summary data-based Mendelian randomization (SMR) analysis for each SNP instrument individually, ad the integrates the b_{xy} estimates of all the SNP instruments by GLS, accounting for the sampling variance in both b_{zx} and b_{yz} for each SNP and the LD among SNPs. We used individual-level genotype data from a subsample of the anorexia nervosa

GWAS to approximate the underlying LD structure to account for LD between the variants in the multi-SNP instrument. Pleiotropy is an important potential confounding factor that could bias the estimate and often results in an inflated test-statistic in Mendelian randomization analysis. We also removed potentially pleiotropic SNPs (i.e., SNPs that have effects on both risk factor and outcome) from this analysis using the heterogeneity in dependent instruments (HEIDI) outlier method[37,95] that detects pleiotropic SNPs at which the estimates of b_{xy} are significantly different from expected under a causal model. The power of detecting a pleiotropic SNP depends on the sample sizes of the GWAS data sets and the deviation of b_{xy} estimated at the pleiotropic SNP from the causal model. Based on this, the overall b_{xy} can be estimated from all the instruments remaining using a generalized least squares approach that takes the LD between the variants and the correlations between their effect sizes into account by modeling them in a covariance matrix. Additionally, GSMR uses the intercept of the bivariate LD score regression to account for potential sample overlap between the GWAS used as instruments for the exposure or outcome[12]. Estimates with binary exposures were converted to the liability scale[40]. Some of these analyses are exploratory because a few utilised GWASs were underpowered (i.e., did not detect ≥10 genome-wide significant independent loci at a p value level of 5×10^{-8}) and we therefore lowered the p value threshold for inclusion, in order to include at least 10 independent SNP instruments as previously recommended[37].

Correction for multiple testing. We calculated the number of independent traits by matrix decomposition (i.e., number of principal components accounting for 99.5% of variance explained) and adjusted our p value threshold accordingly. The first matrix of the main analysis contained all 17 psychiatric traits, all four body composition traits, physical activity, and childhood obesity (Supplementary Data 2). All sex-specific correlations were entered when available. The second matrix comprised all 17 psychiatric traits and all glycemic traits listed in Supplementary Data 6, including their sex-specific correlations. The family-wise Bonferroni-corrected p value threshold for the main analysis including the genetic correlations with body composition traits and physical activity was $p_{\text{Bonferroni}} = 0.05/190 = 2.6 \times$

10^{-4} and the family-wise *p* value threshold for the genetic correlations with glycemic traits was $p_{\text{Bonferroni}} = 0.05/231 = 2.2 \times 10^{-4}$.

URLs. For METAL, see http://csg.sph.umich.edu/abecasis/metal/; for Functional Mapping and Annotation (FUMA), see http://fuma.ctglab.nl/; for Social Science Genetic Association Consortium (SSGAC), see https://www.thessgac.org/, for Complex Traits Genetics lab, see https://ctg.cncr.nl; for International Headache Genetics Consortium, see http://www.headachegenetics.org/, for the Meta-Analyses of Glucose and Insulin-related traits (MAGIC), see https://www.magicinvestigators.org/; for UK Biobank, see https://www.ukbiobank.ac.uk/; for the PTSD working group of the Psychiatric Genomics Consortium, see https://pgc-ptsd.com/; for the Psychiatric Genomics Consortium, see http://www.med.unc.edu/pgc; for the R project, see https://www.r-project.org/, for the Early Growth Genetics Consortium, see https://egg-consortium.org/.

Data availability. Supplementary Data 1 contains all information on data availability, including download links for summary statistics. Summary statistics for the body composition GWAS are available at www.topherhuebel.com/GWAS and the GWAS catalog (www.ebi.ac.uk/gwas/). Most summary statistics for psychiatric disorders are available at www.med.unc.edu/pgc/results-and-downloads/ and for glycemic traits at https://www.magicinvestigators.org/. The data that support the findings of this study are available from UK Biobank (www.ukbiobank.ac.uk). Restrictions apply to the availability of these data, which were used under license for the current study (Project ID: 27546). Data are available for bona fide researchers upon application to the UK Biobank.

Code availability. Analysis code can be accessed on github.com/topherhuebel/ukbgwas. And software can be accessed for BGENIE, at https://jmarchini.org/bgenie/; for BOLT-LMM v2.3.2, at https://data.broadinstitute.org/alkesgroup/BOLT-LMM/; for LDSC, at v1 https://github.com/bulik/ldsc; for METAL, at

http://csg.sph.umich.edu/abecasis/metal/; for, at R 3.4 https://www.r-project.org/, for GSMR, at https://cnsgenomics.com/software/gcta/

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5.8 Authors' contributions

CH, CMB, and GB designed research; CH, HAG, JRIC, KBH, KP, IP, MG, JSN, and TW provided essential materials; CH, HAG, JRIC, KBH, and KP analysed data or performed statistical analysis; CH, HAG, JRIC, and GB wrote paper; CH and GB had primary responsibility for final content. All authors read and approved the final manuscript.

5.9 Competing interests

Dr. Breen has received grant funding from and served as a consultant to Eli Lilly, has received honoraria from Illumina and has served on advisory boards for Otsuka. Dr. Bulik is a grant recipient from and has served on advisory boards for Shire. She receives royalties from Pearson. All interests unrelated to this work. Dr. Coleman, Dr. Gaspar, Ms. Purves, Dr. Hübel, Dr. Hanscombe, Dr. Prokopenko, Dr. Graff, Dr. Ngwa, Dr. Workalemahu, and Dr. O'Reilly declare no competing interests.

6 General discussion, implications, and future directions

The goal of genetic research in anorexia nervosa is to elucidate its underlying biology, as this has the potential to inform clinical and preventive practice through risk prediction, and reveal new therapeutic options by identifying druggable targets[1–3]. This is important as no pharmacological treatments for anorexia nervosa are available, and investigating drug targets based on genetic associations has higher success rates than conventional drug development[4] potentially aiding this underserved population.

Studies within this thesis identified genetic factors that contribute to the risk for developing anorexia nervosa, as well as genetic overlap between anorexia nervosa and psychiatric and metabolic traits, including high-density cholesterol, fasting insulin, and glucose. These findings, in concordance with clinical observations[5,6], lead to a reconceptualisation of anorexia nervosa as a metabo-psychiatric disorder[7], generating new hypotheses.

Given the higher prevalence of anorexia nervosa in women, I use genetically-informed approaches to shed light on biological factors that may increase risk for anorexia nervosa in females (**chapter 4**)[8] and test if these sex-dependent factors also play a role in other psychiatric traits and disorders (**chapter 5**)[9]. Implications and limitations are discussed in detail in each respective chapter and will not be repeated here. The following summary chapter provides a general overview of the key findings, overarching implications, related limitations and ends with directions for future research endeavours.

6.1 Summary of conducted research and relation to published literature

Anorexia nervosa is a severe eating disorder that affects nearly every organ system during acute episodes[6]. Calorie restriction[10] and higher physical activity[11] result in a negative energy balance that leads to the loss of adipose, bone, and muscle tissue[5]. Primarily females develop the disorder[12], but males can be affected, too. Individuals with anorexia nervosa have more highly educated parents[13] and show a genetic liability for higher educational attainment[7,14]. Anorexia nervosa runs in families[15], its reported heritability in twin studies ranges between 32 and 74%[2], and common genetic variants that occur in more than 1% of the population

contribute about 17% to its trait variance[7,14]. It is yet to be demonstrated if rare[16] or copy number variants are also part of the underlying genetic architecture of anorexia nervosa. Likewise, it has yet to be determined if individuals with anorexia nervosa are characterised by an epigenetic profile that differentiates them from healthy controls[17]. Other psychiatric disorders, including obsessive-compulsive disorder[18], anxiety[19], major depressive disorder[20], and autism spectrum disorder[21], are comorbid with anorexia nervosa and coaggregate in families that include individuals with anorexia nervosa. This comorbidity and coaggregation are partially explained by shared genetic liability[7,14].

Chapter 2 refines the anorexia nervosa phenotype by pooling studies assessing body composition traits, their regional distribution, and related biochemical markers in acutely ill and weight recovered anorexia nervosa patients[5]. During the acute phase, anorexia nervosa patients lose up to 50% of their body fat and a substantial degree of fat-free mass and bone mineral mass. Fat-free and bone mineral mass are less responsive to renourishment than fat mass and take longer to fully recover. However, none of the meta-analysed longitudinal studies has follow-up periods sufficient to make robust statements about the full restoration of body composition in anorexia nervosa.

Secondarily, I investigate alterations in body composition with biochemical measures. Few studies report detailed body composition in conjunction with biomarkers, and as such I was able to draw less strong conclusions overall. Comparisons between acutely ill anorexia nervosa patients and controls index lower fat mass-independent fasting insulin and glucose, lower fat mass-dependent leptin, thyroid hormones, and insulin-like growth factor 1, but higher cortisol, and higher fat free-mass dependent cortisol. Comparisons in weight-recovered individuals cannot be calculated because studies investigating biochemistry in weight recovered patients in combination with detailed body composition assessment are scarce.

In **chapter 3**, I report on the largest genome-wide association study of anorexia nervosa conducted to date[7]. We detect genomic regions associated with anorexia nervosa of which four are promising candidates potentially implicated in

the biology of anorexia nervosa as they harbour or are close to one single gene: *CADM1*, *MGMT*, *FOXP1*, and *PTBP2* (though additional fine mapping and functional studies are needed to confirm their role). The association of the region close to *CADM1* with anorexia nervosa is robust with a *p* value of 6.3×10^{-11}, whereas the other single gene regions show associations close to the genome-wide significance threshold of 5×10^{-8}, awaiting confirmation in larger samples. Results generated with the help of interactomics data of the prefrontal cortex and human brain expression data further strengthen these four genes as candidates. At assumed population prevalences of 0.9-4.0%, common genetic variants contribute about 17% of the trait variance in anorexia nervosa in the meta-analyses conducted in **chapter 3**. Common genetic variants associated with anorexia nervosa are pleiotropic and are also positively associated with other psychiatric traits, including schizophrenia, bipolar disorder, major depressive disorder, anxiety disorders, and obsessive-compulsive disorder, mirroring the clinical comorbidity profile and replicating genetic correlations from twin studies as reviewed in **chapter 1**.

Genetic variants associated with anorexia nervosa show pleiotropy with other human traits, including body fat percentage and fat-free mass, and metabolic biomarkers, such as insulin sensitivity and high-density lipoprotein cholesterol. In addition, I contribute to two additional phenotypic meta-analyses, that indicate that acutely ill anorexia nervosa patients exhibit higher high-density lipoprotein cholesterol which tends to normalise with partial weight restoration[22] and higher insulin sensitivity in acutely ill individuals with anorexia nervosa[23]. Both findings mirror the genetic correlations observed in **chapter 3**. Additionally, the genome-wide association study in **chapter 3** shows shared genetic influences between accelerometer measured physical activity and anorexia nervosa, pointing towards a genetic propensity for higher physical activity in anorexia nervosa. Phenotypic characteristics strengthened through these genetic correlations motivate the reconceptualisation of anorexia nervosa as a metabo-psychiatric disorder.

For internal replication, we perform leave-one-out analyses using polygenic risk scores. In this method, one of the cohorts of the meta-analysis is left out and used as the target cohort. Based on the meta-analysis of the other cohorts, we calculate a polygenic risk score in the target cohort and associate it with a

diagnosis of anorexia nervosa. The polygenic risk score analysis explains on average 1.7% in trait variance in each cohort, suggesting that the polygenic signal for anorexia is similar across the cohorts. Further preliminary results suggest that no differences in common genetic architecture between anorexia nervosa with or without binge eating exist or between males and females affected by the disorder.

As the sex effects that contribute to liability for anorexia nervosa are largely unexplained, I examine the potential involvement of genetic factors in the sex bias in anorexia nervosa in **chapter 4**. Using sex-specific genome-wide association studies I demonstrate that the genetic correlation between body fat percentage and anorexia is sex-dependent and stronger in females than in males, suggesting that a female-dependent set of genomic variants may contribute to the sex bias in anorexia nervosa[8]. Enrichment analysis of the female body fat percentage genome-wide association study implicate brain tissue in its regulation which points towards central nervous system pathways.

The molecular genetic correlations identified in **chapter 3** replicate genetic overlap implicated by bivariate twin studies between anorexia nervosa and depression[24], anxiety sensitivity[25], and obsessive-compulsive disorder[18] and family studies that show familiality between anorexia nervosa and schizophrenia (R. Zhang, personal communication). In **chapter 4** I test if any of these genetic correlations with psychiatric traits is sex-dependent. The comparison between the female and the male genetic correlation suggests sex differences, however when formally tested using the jackknife approach, the differences do not reach statistical significance. Potentially, male-dependent genetic variants associated with obsessive-compulsive disorder and anxiety may contribute to the aetiology of anorexia nervosa, but the evidence presented in **chapter 4** is insufficient[8], making analysis with larger samples necessary. The findings should be followed up because obsessive-compulsive disorder in males[18] and paternal panic disorder[19] are identified as risk factors for anorexia nervosa in longitudinal register studies.

The substantial genetic overlap across body composition, physical activity, glycaemic traits, lipid-related traits and anorexia nervosa was unexpected. To understand the genetic relationship between these traits and 17 behavioural and

psychiatric disorders, I perform a cross-disorder analysis[9] in **chapter 5**. After controlling for addiction-related behaviours such as smoking and alcohol consumption, I identify two groups of psychiatric traits that are genetically correlated with body composition traits. The first group includes anorexia nervosa, schizophrenia, obsessive-compulsive disorder, and education years, which are negatively genetically correlated with fat mass and fat-free mass, whereas the second includes attention deficit hyperactivity disorder (ADHD), alcohol dependence, insomnia, and heavy smoking, which are positively genetically correlated with fat mass and fat-free mass.

Anorexia nervosa and obsessive-compulsive disorder are the only psychiatric disorders that share genetic variants with physical activity, whereas only anorexia nervosa shares genetic variants with glycaemic traits. Against expectations and in contrast to clinical observations, neither major depressive disorder correlates genetically with body fat percentage nor ADHD with physical activity. Additionally, ADHD is the only psychiatric disorder that genetically correlates with obesity in childhood, indicating shared genetic influences early in life. Our investigation positions anorexia nervosa uniquely among all other psychiatric disorders due to its negative genetic overlap with glycaemic traits and positive overlap with high-density lipoprotein cholesterol-related biomarkers.

In **chapter 3** and **4,** I provide evidence that the genetic overlap between psychiatric disorders and body mass index is age-dependent, although body mass index is genetically correlated across the lifespan. Body mass index measured in childhood, adolescence, and young adulthood is not genetically correlated with anorexia nervosa (or any other psychiatric disorders), whereas body mass index in late adulthood is. For the future, year-by-year sex-specific genome-wide association studies of body mass index during the first 40 years of life could identify age period-specific genomic associations. Subsequently, genetic correlation analysis between the year-by-year genome-wide studies could be used to test the hypothesis of genetic innovation for body mass that I forward in **chapter 4**. Genetic correlations between these year-by-year body mass index genome-wide association studies and psychiatric disorders can identify the exact time period when the genetic overlap occurs and, thus, index sensitive periods for preventive strategies.

Our causal inference analysis using Mendelian randomisation identifies schizophrenia, anorexia nervosa, and higher education as causal risk factors for lower fat mass and higher body fat percentage as a causal risk factor for ADHD and heavy smoking. I did not identify a causal relationship from body fat percentage to anorexia nervosa. However, the conclusions that can be drawn from these analyses are limited by the—as yet—marginal power of the available anorexia nervosa genome-wide association data.

6.2 Implications

Anorexia nervosa is a psychiatric syndrome that comprises several symptoms and no biomarkers are available to diagnose the disorder. Twin studies suggest shared biological underpinnings between anorexia nervosa and bulimia nervosa. Through genetically-informed techniques, we may be able to explore this shared liability between eating disorders, refine the anorexia nervosa phenotype, and identify anorexia nervosa-specific biological pathways. This may enable us to more easily detect biomarkers for diagnosis and risk prediction.

6.2.1 Implications for the conceptualisation of anorexia nervosa

Biological overlap between eating disorders. The biological overlap amongst eating disorders is mostly unexplored. One bivariate twin study indicates shared genetic factors between anorexia and bulimia nervosa[26], but other correlations are not yet calculated. With the help of twin and genome-wide association studies pairwise genetic correlations between bulimia nervosa, binge-eating disorder, purging disorder, and avoidant restrictive food intake disorder should be calculated to clarify if a shared genetic vulnerability exists.

After obtaining genome-wide association results from each eating disorder, their genetic covariance structure can be modelled jointly and be used to identify underlying latent factors. Sophisticated techniques have been developed to model genomic covariance structure between more than one trait called genomic structural equation modelling[27]. After the identification of latent factors, it is possible to perform a genome-wide association study on these factors which can be used to identify traits that may represent this latent trait through genetic

correlation analysis even if the latent trait was not directly measured. Genomic structural equation modelling has the potential to discover previously unknown traits that may be implicated in the aetiology of eating disorders

Eating behaviour as a continuum. Proposals are made to apply a continuous model to disordered eating behaviour[28,29] akin to that used for autism spectrum disorder. Disordered-eating behaviour may represent endophenotypes of eating disorders, including overeating, binge eating, undereating, restrictive eating, fussy eating, purging behaviour, and appetitive traits as measured by the Adult Eating Behaviour Questionnaire (AEBQ) such as food responsiveness[30]. These continuous traits should be tested for associations with genetic variants: If eating disorder diagnoses and continuous eating behaviour traits were genetically correlated, this would provide first evidence that continuous eating behaviour traits and eating disorders share underlying biology, strengthening the proposal of a spectrum of disordered eating. Additionally, early childhood undereating is associated with anorexia nervosa[31], but it is unclear if this early undereating represents a prodrome or an independent risk factor for anorexia nervosa. Genetic correlation or polygenic score analyses between childhood undereating and anorexia nervosa may elucidate their biological relationship, helping to delineate a prodrome from a risk factor.

Cognitive endophenotypes. Anorexia nervosa-associated psychological traits like problems in cognitive set shifting[32], perfectionism[33], or body image disturbances[34] should be examined as potential endophenotypes. For example, a psychotic continuum from overvalued ideas, over cognitive bias, to uncorrectable delusions is posited[35]: Individuals with anorexia nervosa exhibit distorted body perception and overvalued ideas about food items[36]. Cognitive biases are a cross-diagnostic symptom of several psychiatric disorders, including schizophrenia, obsessive-compulsive disorder, depression, and anorexia nervosa, and an investigation of the psychotic/delusional spectrum could bridge the gap in our understanding of the relationship between these disorders. Small genome-wide association studies of body dissatisfaction and drive for thinness exist, but bivariate analysis do not reveal genetic correlations between these cognitions and

anorexia nervosa (Z. Yilmaz, personal communication). This, however, may be a power issue. I am collecting data from available cohorts to perform a larger meta-analysis and repeat these analyses.

Anorexia nervosa-specific genetic factors. A general liability to psychopathology called the "p factor" is postulated[37,38], reflecting an underlying genetic vulnerability that is shared across psychiatric disorders[27]. If this holds true, it will be important to identify disorder-specific factors that lead to the expression of anorexia nervosa. To identify anorexia nervosa-specific genetic factors genome-wide association studies comparing individuals with anorexia nervosa with individuals with other psychiatric disorders, such as anxiety or major depressive disorder should be performed. Alternatively, genomic techniques, such as multi-trait conditional and joint analysis[39] (mtCOJO, explained in **chapter 3**) or genomic structural equation modelling[27], have the ability to adjust genome-wide association summary statistics of anorexia nervosa for traits like depression. This adjustment may show if genome-wide associations are dependent, for instance, on depression. These approaches should also be employed to compare anorexia nervosa to other disordered-eating behaviours and eating disorders, such as binge-eating disorder, to uncover eating disorder-specific genetic risk factors.

Relationship between body mass index and anorexia nervosa. Anorexia nervosa is negatively genetically correlated with body mass index[7,14] which suggests that anorexia nervosa or a component of it may be a part of the opposite bookend to obesity[40]. Traditionally, however, persistent thinness (i.e., constitutional thinness) is viewed as the opposite to obesity. Individuals with constitutional thinness take measures to gain weight without success but show no disordered-eating behaviour. Persistent thinness does not genetically correlate with anorexia nervosa at current genome-wide association study sample sizes[41]. Thus, a genome-wide association study comparing individuals with anorexia nervosa with individuals with persistent thinness or adjusting the anorexia nervosa genome-wide association study for persistent thinness may identify anorexia nervosa-specific genetic associations and clarify some of the metabolic correlations. This approach may overcome the confounding through body mass.

Additionally, comparing extreme phenotypes like extreme obesity with anorexia nervosa by performing a genome-wide association study could improve our understanding of biological mechanisms that contribute to the regulation of body weight at the extremes.

Identification of subtypes. The anorexia nervosa phenotype could further be refined by identifying potential subtypes. To achieve this, individuals with anorexia nervosa could be clustered by their individual genetic liability to traits. Their individual genetic liabilities can be expressed by polygenic scores, calculated as a sum of an individual's genome-wide genotypes multiplied by corresponding effect sizes obtained from genome-wide association summary statistics for other traits. The traits used for clustering could be preselected based on the genetic correlations that I identified in **chapter 3** in addition to polygenic scores of eating behaviour. Not only genetic variables but also environmental markers, including hormone concentrations, questionnaire responses, or metabolome data could be used to identify subtypes of anorexia nervosa[42,43]. Unsupervised machine learning approaches, including clustering techniques and neural networks[44] that group genetic and environmental variables based on their relationships to each other may detect clusters (i.e., classes) within the anorexia nervosa cases. These models assign each individual a probability of class membership. Based on the variables that contribute to the generation of a class, these clusters can be interpreted: It may be possible to identify a subtype of anorexia nervosa that is more influenced by metabolic factors whereas another subtype may be associated with the societal pressure to be thin.

In summary, we change the way anorexia nervosa is commonly perceived and provide evidence for metabolic and psychiatric components of the disorder. With the help of genetically-informed techniques, we will be able to better understand the shared and disorder-specific factors of eating disorders, especially anorexia nervosa, as sample collection for other eating disorders is underway. We may be able to identify latent traits (i.e., endophenotypes) that are associated with anorexia nervosa, and elucidate the role of dysregulated body composition in anorexia nervosa.

6.2.2 Clinical implications

Strengthening the evidence for a genomic component in anorexia nervosa helps to lower the stigma that surrounds the disorder[45–50]. Knowing that a part of the disorder may be due to dysregulated human biology that arises from an interaction of genetic and environmental factors may alleviate personal blaming in affected individuals and facilitate coping. The knowledge of an underlying biology can be incorporated in psychoeducation to provide patients and their families with a better understanding of anorexia nervosa.

If the finding of higher insulin sensitivity detected through genetic correlation analyses is robust following replication, it would be important for clinicians to be vigilant of glycaemic fluctuations and metabolic alterations during the renourishment process. Furthermore, continuous glycaemic monitoring in intermediate or intensive care settings may prevent life-threatening hypoglycaemic shocks in severely underweight and hospitalised patients with anorexia nervosa.

Additionally, patients with anorexia nervosa may carry a genetic propensity to higher physical activity. This may be important for inpatient treatment during which bed rest is commonly used as part of nursing management. Bed rest, however, shows considerable side effects, such as lower heart rate, impaired bone turnover, and a higher risk of infection. Furthermore, enforcement of bed rest is associated with psychological harm[51]. Future studies are needed to optimise physical activity in the treatment of patients with anorexia nervosa and understand higher physical activity as part of the disorder.

6.2.3 General methodological comments

Sample size. The identification of meaningful effect sizes in studies depends on statistical power which stems from adequate sample sizes. First, the majority of the biomarker studies that are meta-analysed in **chapter 2** are very small, leading to an increased likelihood of reporting false positives. Even after pooling and meta-analysing samples some comparisons include less than 100 cases of anorexia nervosa. Some reviews report lower testosterone in anorexia nervosa[6], but our meta-analysis does not support this claim[5]. Second, the sample size of our genome-wide association study in **chapter 3** with about 17,000 cases

and 55,000 controls seems huge; however, in terms of genome-wide association studies it is relatively modest. Further increases of the sample size should lead to accelerated genomic discovery, which will provide us with more power for pathway and enrichment analyses to elucidate disordered biology.

Validity of self-reported diagnoses. To collect these samples in reasonable time periods, online recruitment has become popular[52,53]. The ED100K questionnaire[53] is especially designed for this purpose. Validation of the questionnaire through follow up interviews is underway. However, self-reported diagnoses and diagnoses derived from questionnaires via algorithms may be confounded by recall bias and lead to false positives. A considerable part of the anorexia nervosa sample ascertained by the Psychiatric Genomics Consortium is clinically diagnosed. Therefore, it is possible to perform two separate genome-wide association studies: one on clinically ascertained cases and one on self-reported diagnoses. Subsequently, the genetic correlation between these genome-wide association studies can be calculated to test if both ways of diagnostic ascertainment index the same underlying biology. This approach can function as an internal validation of the ascertainment process.

Imputation panel. As outlined in **chapter 1**, the genome-wide coverage is an important factor for the success of genome-wide association studies. During the last two years, better and denser imputation reference panels were generated, including panels from the Haplotype Reference Consortium (HRC)[54] and Trans-Omics for Precision Medicine (TOPMed)[55] consortium, which should be used for imputation of the next eating disorders genome-wide association studies. With the help of these reference panels, it will be possible to detect rarer genomic variants with frequencies below 1% that may be associated with an eating disorder[56]. Alternatively, exome or whole genome sequencing can be applied to directly genotype rarer variants and increase the coverage across the genome; however, these approaches need far larger sample sizes than the detection of common genomic variants and are still costly, but prices are expected to drop. Additionally, copy number variants, structural variants that are longer than 200 kb, should be tested for association with anorexia nervosa as early attempts were unsuccessful[57]. However, associations are less expected because individuals carrying copy number

variants often present with more severe phenotypes that include developmental delay and somatic malformations[58].

Replication. At the time of submission of this thesis, all collected cases of anorexia nervosa are included in the genome-wide association study in **chapter 3** to optimise power and facilitate region discovery. However, in the future, if enough samples are amassed, replication should be attempted.

Underserved populations. The genome-wide association study in **chapter 3** was only performed on individuals of European ancestry. Multi-ancestry genome-wide association studies provide additional power to detect associations[59]. Statistical simulations that compare muli-ancestry genome-wide association studies with European-only show greater power for the detection of association for polymorphisms with frequencies lower than 5%[60]. Therefore, multi-ancestry samples represent an underused resource for the detection of genome-wide associations[61]. Moreover, associations detected in non-European samples would further aid underserved populations, such as African and admixed South American populations.

Males with anorexia nervosa are underrepresented in the meta-analysis of body composition traits and biomarkers (**chapter 2**) as well as in the genome-wide association study (**chapter 3**). It is important to optimise participant recruitment for males by developing gender-sensitive measures[62] and using male-specific recruitment strategies, potentially advertising in gyms, sports clubs, or sexual health clinics.

Conditional genetic effects and interactions. The genome-wide association study in **chapter 2** is based on an additive genetic model that assumes that each polymorphism has an independent effect on the phenotype that can be summed with the effects of all other polymorphisms. However, it is possible that the effects or different genetic variants may be dependent on each other. Conditional analysis using linear mixed models that fit polymorphisms jointly may detect conditional effects.

In summary, with larger sample sizes, improved imputation, and inclusion of admixed populations, we will boost statistical power and accelerate the identification of genomic variants associated with anorexia nervosa but also other eating disorders.

6.3 Future directions

We have made significant progress in elucidating the underlying biology of anorexia nervosa, but we are still lagging behind other psychiatric disorders like schizophrenia[63] or major depressive disorder[64] for which sample sizes in the 100 thousands have been reached. Methodology in statistical genetics is rapidly advancing which opens up new avenues to modelling genomic variants even at frequencies lower than 1%. We must take further steps to use up-to-date methodology to identify actionable genetic variants but also explore environmental risk factors through genetics, using polygenic scores and Mendelian randomisation. Thus, I outline ideas and suggestions for future projects.

6.3.1 Understanding aetiology: Longitudinal multi-omics approach

If we assume that a general liability for psychopathology exists, it is important to unravel the anorexia nervosa-specific factors that lead to the expression of the phenotype. Potentially, individuals with anorexia nervosa carry several polygenic liabilities, for instance, for elevated high-density lipoprotein, for higher insulin sensitivity, and for more negative cognitive bias that interact with each other and act in concert with environmental factors, such as sex hormone concentrations and dieting behaviour. Several constellations of these factors may create an individual risk profile that during a sensitive developmental period can trigger the onset of the disorder.

This hypothetical model provides the basis for future research: Longitudinal studies that use a multi-omics approach are needed. They should sample genetic and epigenetic variation, gene expression, metabolomics, lipidomics, proteomics, and sex hormone concentrations which should be modelled jointly. Potentially, individuals at high risk could be preselected through higher polygenic risk scores or positive family history to reduce study costs. Measurements could be sparse in childhood, but should be conducted more often during adolescence. First preliminary studies, to which I contributed, show alterations in the metabolic profile of children that go on to develop anorexia nervosa in adolescence at the age of 7 years[65].

Until rich longitudinal data is available causal risk factors can be identified through causal inference methods such as Mendelian randomisation (explained in

detail in the methods section of **chapter 5**). Instrumental variables are used to expose individuals hypothetically to potential risk factors. With the help of this method, I present preliminary results that anorexia nervosa is a risk factor for lower body fat. Mendelian randomisation should be used to examine a wider range of potential risk factors for anorexia nervosa after more robust genome-wide associations have been identified.

The approach of identifying individuals who are at high risk of developing anorexia nervosa due to high polygenic scores could also be applied in large longitudinal studies that measure a variety of variables throughout development. Supervised machine learning may help to identify variables that are associated with developing anorexia nervosa in individuals with either low or high polygenic risk score. This approach may also help to identify protective factors.

6.3.2 Preventative strategies: Risk prediction

Polygenic risk scores can also be used for risk prediction. However, a polygenic score can maximally explain the same trait variance in an external sample as in the discovery sample[66]. A polygenic score derived from the genome-wide association study in **chapter 3** would maximally explain 17% of trait variance in an external sample. To explain more trait variance, additional variables must be incorporated in the model, such as polygenic scores for different traits or environmental variables. Such a combined risk score may stratify individuals depending on their individual risk compared to the risk in the underlying population. With the help of these likelihoods, individuals at high risk could be directed towards screening programmes.

6.4 Conclusion

Given the rich data that were collected and analysed, we present evidence for a metabolic component of anorexia nervosa that is partially due to shared underlying genetics. This new understanding of anorexia nervosa as a metabo-psychiatric disorder opens up new avenues for future research strategies and underscores the need to collect large international samples with deep phenotyping of not only psychological traits, but also metabolomic, proteomic, and lipidomic markers in anorexia nervosa patients. We strengthen the perspective that anorexia nervosa has a biological component which reduces the stigma associated with anorexia nervosa and set an example for future research on other eating disorders.

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Appendix 1 Epigenetics in eating disorders: a systematic review

This appendix, synthesising studies on epigenetics in eating disorders, is presented as a published paper. It is an exact copy of this publication.

Hübel, C.*, Marzi, S. J.*, Breen, G., & Bulik, C. M. (2019). Epigenetics in eating disorders: a systematic review. *Molecular Psychiatry*, *24*(6), 901–915.

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EXPERT REVIEW

Epigenetics in eating disorders: a systematic review

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Abstract

Eating disorders are complex heritable conditions influenced by both genetic and environmental factors. Given the progress of genomic discovery in anorexia nervosa, with the identification of the first genome-wide significant locus, as well as animated discussion of epigenetic mechanisms in linking environmental factors with disease onset, our goal was to conduct a systematic review of the current body of evidence on epigenetic factors in eating disorders to inform future directions in this area. Following PRISMA guidelines, two independent authors conducted a search within PubMed and Web of Science and identified 18 journal articles and conference abstracts addressing anorexia nervosa ($n = 13$), bulimia nervosa ($n = 6$), and binge-eating disorder ($n = 1$), published between January 2003 and October 2017. We reviewed all articles and included a critical discussion of field-specific methodological considerations. The majority of epigenetic analyses of eating disorders investigated methylation at candidate genes ($n = 13$), focusing on anorexia and bulimia nervosa in very small samples with considerable sample overlap across published studies. Three studies used microarray-based technologies to examine DNA methylation across the genome of anorexia nervosa and binge-eating disorder patients. Overall, results were inconclusive and were primarily exploratory in nature. The field of epigenetics in eating disorders remains in its infancy. We encourage the scientific community to apply methodologically sound approaches using genome-wide designs including epigenome-wide association studies (EWAS), to increase sample sizes, and to broaden the focus to include all eating disorder types.

Introduction

Eating disorders are serious illnesses associated with significantly reduced health-related quality of life [1, 2]. Our current understanding of their etiology is piecemeal and the evidence base for their treatment, especially anorexia nervosa (AN) in adults, is inadequate [3]. Over the past two decades, family, twin, and adoption studies have robustly shown that eating disorders reflect the pattern of complex trait inheritance being influenced by both genetic and environmental factors. Twin-based heritabilities for AN range from 48 to 74%, for bulimia nervosa (BN) from 55 to 62%, and for binge-eating disorder (BED) from 39 to 45% [4]. A genome-wide association study of AN has yielded the first genome-wide significant locus on chromosome 12—a chromosomal region previously associated with autoimmune diseases including type 1 diabetes [5]. AN, furthermore, shows significant genetic correlations with various psychiatric, personality, and metabolic phenotypes, including schizophrenia, neuroticism, glucose metabolism, and lipid metabolism. This panel of findings has encouraged a reconceptualization of AN as both a metabolic and psychiatric disorder [6]. At the same time, epigenetic mechanisms have garnered much interest, offering an added

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layer of gene regulatory information, which could link external and internal environmental stimuli as well as non-coding genetic variation with transcriptional consequences, altering downstream phenotypes [4, 7–9]. Together with enhanced understanding of the genetic variants underlying heritable disease risk in eating disorders, epigenetics has the potential to aid in disentangling the molecular genetic pathways that contribute to the development and progression of the illnesses.

Epigenetics

In the context of this review, epigenetics refers to various biochemical mechanisms giving rise to changes in gene regulation, which are either heritable or characterized by long-term stability [10]. Biologically, epigenetic mechanisms can be categorized into three groups: DNA modifications, histone modifications, and non-coding RNA (for details, see Fig. 1). DNA modifications are chemical modifications that bind to the DNA itself. Histone proteins constitute the cores around which DNA is wrapped in the cell nucleus. They can exert an effect on gene regulation by altering the accessibility of DNA sequences [10]. Finally, non-coding RNAs—expressed transcripts which do not code for proteins—have widespread effects on gene regulation via mechanisms including post-transcriptional silencing [11, 12] or chromatin remodeling [13].

DNA methylation is the most widely studied epigenetic mechanism in the context of complex traits thus far and disease-associated methylomic dysregulation has been reported for a number of psychiatric disorders, including schizophrenia [14, 15], Alzheimer's disease [16, 17], and autism spectrum disorder [18, 19]. In addition to DNA methylation, its oxidized derivatives constitute further DNA modifications, with DNA hydroxymethylation generating increasing interest in the context of neuropsychiatric disease, due to its enrichment in the human brain [20, 21]. While historically defined as occurring independent of the DNA sequence, recent work has provided evidence for widespread effects of genetic variants on epigenetic states. In particular, methylation quantitative trait loci (mQTLs) are increasingly being characterized: single nucleotide polymorphisms (SNPs) that exert influence on the methylation state of a CpG site, usually in close vicinity to the SNP [22, 23].

Unlike the genome sequence, epigenetic marks are dynamic and can vary across cell- and tissue-types, age and development, and can be subject to environmental stimuli including medication and stress (Fig. 2). Perhaps most strikingly, this has been shown for tobacco smoking, which was found to have considerable effects on DNA methylation across several genomic regions [24]. Similarly, epigenetic profiles are highly correlated with chronological age and an accurate predictor of age has been derived based on the DNA methylation profiles of only around 300 CpG sites [25]. In this sense they are more accurately characterized as intermediate biological phenotypes and are susceptible

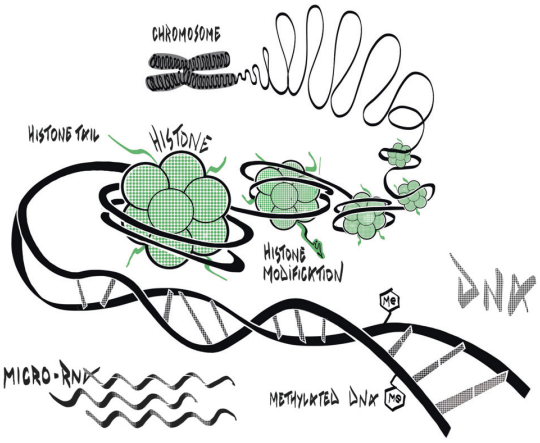

Fig. 1 The epigenetic profile of a human cell comprises several epigenetic mechanisms: **a** DNA methylation is the most prominent and prevalent DNA modification characterized by an addition of a methyl-group to cytosine in the context of cytosine-guanine dinucleotides (i.e., CpG sites). **b** Histone proteins compact chromosomal DNA in the nucleus of the cell and regulate gene expression. Histone modifications are chemical modifications to the N-terminal histone tails, which extend out of the nucleosome complex. An increasing number of modifications to amino acids in the histone tails are being identified, including methylation, acetylation, and phosphorylation. These modifications are characterized by tissue specificity and are highly correlated with different chromatin states. **c** Non-coding RNAs are expressed transcripts that do not code for proteins. They can affect gene regulation by binding to transcripts and inhibiting their translation to proteins (i.e., post-transcriptional silencing) or by guiding the positioning of nucleosomes along the genome and thereby altering DNA accessibility. Designed by Vinícius Gaio, London, UK

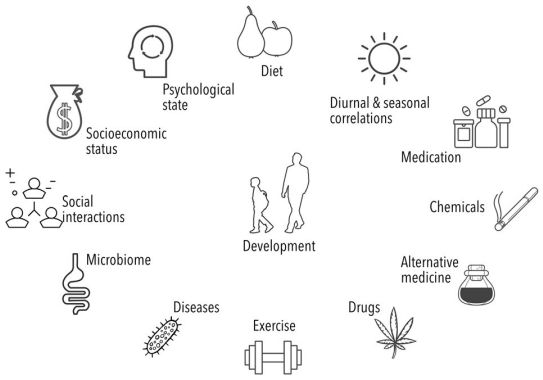

Fig. 2 Potential factors and environmental confounders influencing epigenetic profiles. The assessment of these factors should ideally be included in the design of a study investigating epigenetic profiles

to confounding and other problems faced in traditional observational studies. This phenotypic feature of epigenetic profiles means that sources of variation or confounding need to be taken into account in the experimental design and statistical analyses [26, 27]. For example, if all individuals in the control group are older than the affected individuals, an epigenome-wide association study (EWAS) may detect epigenetic differences between the two groups related to ageing, rather than differences associated with disease status.

Several characteristics of eating disorders support investigation into the potential contribution of epigenetic factors, including sex differences (i.e., females are ~8 times more likely to suffer from AN or BN than males) [28], periods of increased risk of onset (i.e., particularly in adolescence and young adulthood) [29], and reported discordance between monozygotic twins [30, 31]. Eating disorders are associated with early life stress [32] and emerging evidence links early life stress with epigenetic profiles [33]. Empirical evidence confirming this association in humans is limited due to the low availability of brain tissue and the scarcity of large longitudinal studies that collect information on early traumatic experiences and biological samples enabling epigenetic analysis [34]. The largest study of early-life adversity and DNA methylation in blood published to date identified no significant differential methylation [35]. These characteristics suggest that the interaction of genetic risk factors and environmental stressors, can contribute to the onset of eating disorders and make them an excellent target for the examination of epigenetic effects on appetite regulation and eating behavior.

New technical advances in genetic and epigenetic research, including array-based genome-wide analysis methods, have led to rapid accumulation of evidence in the field of psychiatric epigenetics and could serve to expedite understanding of the biology of eating disorders and to identify more efficient treatment options [36]. Therefore, we performed a systematic review including a critical appraisal of the recent body of evidence of epigenetic research in eating disorders to reflect on past research and its limitations and offer guidance for future investigations.

Method

Search strategy

Our systematic literature review was conducted according to PRISMA guidelines [37]. We conducted an exhaustive literature search from 16.10.2017 until the 30.10.2017 using the electronic databases PubMed and Web of Science with a time limitation starting with articles published after 01.01.2003 marking the first published paper on epigenetics of eating disorders. We used following key search terms including (anorexia OR bulimia OR "binge-eating disorder" OR "eating disorder") AND (epigenetics OR methylation OR histone OR "non-coding RNA"). The search was repeated by the co-primary author to avoid selection bias. Furthermore, we screened the references of published articles and reviews. Our search results including the selection process are presented in Fig. 3 according to PRISMA guidelines.

Selection criteria

Our inclusion criteria were as follows:

a. Studies investigating humans only
b. Any age group
c. Clinical diagnoses of AN, BN, or BED according to Diagnostic and Statistical Manual of Mental Disorders versions IV or 5 and their revisions [38] or International Classification of Diseases [39]
d. Investigation of any type of epigenetic mechanism: methylation, histone modification, non-coding RNAs
e. Published after 01.01.2003 (date that the first article on epigenetics of eating disorders appears in the literature)
f. Study includes a control group or comparison group
g. Publications in any language

Data extraction

We extracted following information from every identified study:

a. Author
b. Publication year
c. Sample including gender and age
d. Follow-up period
e. Diagnostic criteria
f. Participant screening and exclusion criteria
g. Number of cases (AN, BN, BED)
h. Number of controls
i. Matching of cases and controls
j. Outcome variables (Genome-wide methylation level, candidate genes, number of CpG sites)
k. Covariates
l. Tissue
m. Correction for multiple comparison
n. Laboratory methods
o. Limitations

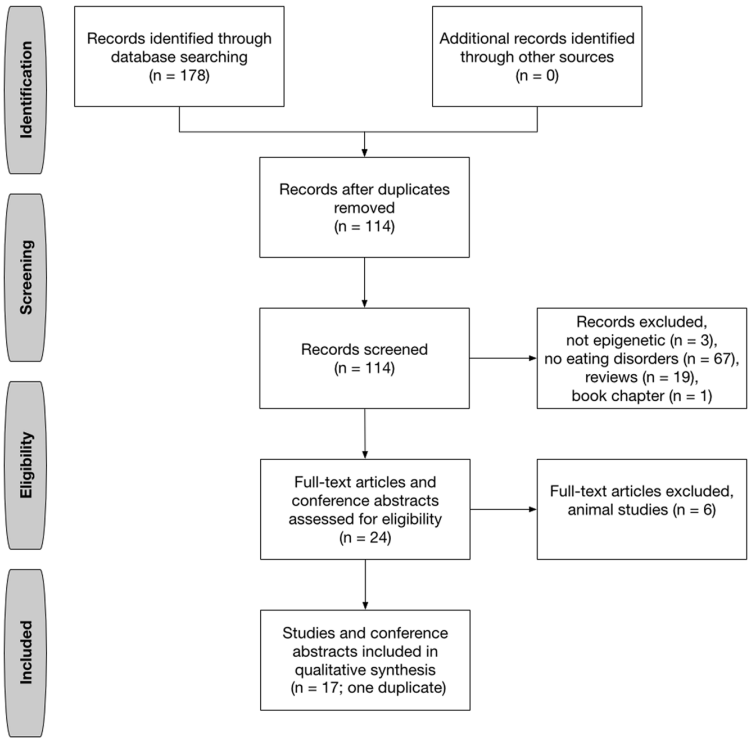

Fig. 3 PRISMA flow diagram of study selection

Quality of evidence assessment (GRADE criteria)

We used the GRADE criteria to assess the quality of evidence of each outcome in our review against eight criteria, including risk of bias, indirectness, inconsistency, imprecision, and publication bias [40]. The quality is graded high, moderate, low, or very low and reflects the degree of confidence in the reviewed effects. We assessed the quality of evidence for the three outcomes based on their study design: global methylation level, all candidate genes together, and EWAS associations.

Results

A total of 178 papers were identified by our search terms. We excluded 67 studies because they did not cover eating disorders, six did not investigate humans, 19 were reviews, one was a book chapter, and three did not examine epigenetic mechanisms. This resulted in 16 published studies and two conference abstracts on epigenetics that met our predetermined inclusion criteria (Fig. 3). One full-text article was a duplicate of a conference abstract, resulting in 17 studies. To our knowledge these represent all published studies and conference abstracts investigating epigenetics in eating disorders that were available at the close of our search in October, 2017. We contacted authors of conference abstracts for additional information on their studies (Table 1).

Recent body of evidence

To date, 17 studies on the epigenetics of eating disorders have been published of which four investigated global DNA methylation levels, 13 investigated candidate genes, and three used microarray-based technologies to profile DNA methylation across the human genome. One study design was longitudinal, but within this study one time point was selected and analysed cross-sectionally [41]. All other studies were purely cross-sectional in design and analysis. Studies primarily investigated young adult females and focused exclusively on DNA methylation and some also investigated expression levels, but did not investigate other epigenetic mechanisms, such as histone modifications or non-coding RNAs (Table 1). The studies show extensive sample overlap as four studies are part of the homocysteine and DNA methylation in eating disorders (HEaD) study [42–45], two studies recruited inpatients at the Universitätsmedizin Charité Berlin, Germany [46, 47], and four studies recruited at the Douglas Institute Eating Disorders Program in Montreal,

Table 1 Overview of included studies. Gene names are those used in the articles and additionally standardized gene names according to www.genenames.org. All studies were cross-sectional in their statistical analysis

Author (Year)	Sample				Medicated	Tissue/cell type - Correction - Suitability - Limitation	Methylation results				Assessed confounds and exclusion criteria	Biological hypothesis (PMID) → mechanistic or potential biomarker study
	N	Female	Age (SD) [years]	Diagnoses			Global methylation	AN	BN	BED		
Frieling (2007)	AN: 22 BN: 24 CO: 30	100% 100% 100%	26.5 (10.3) 25.8 (7.7) 22.0 (4.8)	DSM-IV	n.a.	Whole blood - uncorrected - proxy tissue - not mentioned		↓	↔		**Confounds**: Homocysteine **Exclusion**: None	Elevated homocysteine blood levels in 18 AN cases (PMID: 15937640) → mechanistic hypothesis of homocysteinemia altering methylation levels
Saffrey (2014)	AN: 10 CO: 10	100% 100%	21.5 (10.2) 23.1 (9.5)	n.a.	n.a.	Buccal cells - uncorrected - proxy tissue - discussed		↔			**Confounds**: None **Exclusion**: None	No hypothesis, only prior epigenetic studies
Tremolizzo (2014)	AN: 32 CO: 13	100% 100%	15.5 (1.4) 16.3 (1.3)	DSM-IV-TR	53.2%	Whole blood - uncorrected - proxy tissue - not mentioned		↓			**Confounds**: Leptin, homocysteine, vitamin B12, folate, cortisol, testosterone, progesterone, estradiol, dehydroepiandrosterone, CDI, STAI-Y S & T, EDI-3 **Exclusion**: All: hematological or hepatic disorders, cancer, recent infections or surgery, <14 and >18 years, alcohol abuse CO: neurological or psychiatric disorder, medication	No hypothesis, only prior epigenetic studies → biomarker study for early diagnosis
Booij (2015)	AN: 29 CO: 15	100% 100%	22.7 (5.9) 24.2 (5.8)	DSM-5	~70%	Lymphocytes - not necessary - proxy tissue - mentioned		↑			**Confounds**: None **Exclusion**: None	No hypothesis, only prior epigenetic studies

Author (Year)	Sample				Medicated	Tissue/cell type - Correction - Suitability - Limitation	Methylation results				Assessed confounds and exclusion criteria	Biological hypothesis (PMID) → mechanistic or potential biomarker study
	N	Female	Age (SD/range) [years]	Diagnoses			Candidate genes	AN	BN	BED		
Frieling (2007)	AN: 22 BN: 24 CO: 30	100% 100% 100%	26.5 (10.3) 25.8 (7.7) 22.0 (4.8)	DSM-IV	n.a.	Whole blood - uncorrected - proxy tissue - not mentioned	*SNCA* *HERP*	↑ ↔	↔ ↔		**Confounds**: Homocysteine **Exclusion**: None	Elevated homocysteine blood levels in 18 AN cases (PMID: 15937640) → mechanistic hypothesis of homocysteinemia altering methylation levels
Frieling (2008)	AN: 22 BN: 22 CO: 30	100% 100% 100%	22 (18–51) 23 (18–42) 21 (19–43)	DSM-IV	n.a.	Whole blood - uncorrected - proxy tissue - partially discussed	*ANP* Vasopressin	↔ ↔	↑ ↔		**Confounds**: Purging, binge eating, age, BMI, duration of illness, electrolytes, hematocrit, creatinine **Exclusion**: None	Elevated vasopressin in 10 AN cases (PMID: 10960163) → mechanistic hypothesis of the dysregulation of fluid homeostasis
Frieling (2009)	AN: 20 BN: 23 CO: 26	100% 100% 100%	26.4 (10.6) 25.9 (7.9) 21.3 (2.2)	DSM-IV	n.a.	Whole blood - uncorrected - proxy tissue - not mentioned	*CNR1/CB1* *CB2*	↔ n.a.			**Confounds**: None **Exclusion**: None	Elevated endocannabinoids in 10 AN cases (PMID: 15841111) → mechanistic hypothesis of altered endocannabinoid signaling
Frieling (2010)	AN: 22 BN: 24 CO: 30	100% 100% 100%	26.5 (10.3) 25.8 (7.7) 22.0 (4.5)	DSM-IV	n.a.	Whole blood - uncorrected - proxy tissue - discussed	*SLC6A3/DAT* *DRD2* *DRD4*	↑ ↑ ↔	↑ ↔ ↔		**Confounds**: None **Exclusion**: All: high coffee consumption, alcohol abuse, medication, endocrinological conditions, other diseases (i.e., thromboembolic, diabetes mellitus, cardiovascular diseases) CO: any medical or psychiatric condition	Six recovered AN cases showed lower levels of homovanillic acid in CSF (PMID: 10481833) Increased binding of [^{11}C]-raclopride at cerebral D2/D3 receptors in 10 recovered AN patients (PMID: 15992780) → mechanistic hypothesis of disturbed dopaminergic signaling

Table 1 (continued)

Author (Year)	Sample				Medicated	Tissue/cell type - Correction - Suitability - Limitation	Methylation results				Assessed confounds and exclusion criteria	Biological hypothesis (PMID) → mechanistic or potential biomarker study
	N	Female	Age (SD/range) [years]	Diagnoses			Candidate genes	AN	BN	BED		
Ehrlich (2010)	AN: 31 AN-Rec: 30 CO: 30	100% 100% 100%	16.4 (1.3) 19.3 (3.0) 16.4 (1.5)	DSM-IV	0%	Whole blood - uncorrected - proxy tissue - discussed	*POMC*	↔			**Confounds**: Age, duration of illness, BMI, leptin, cortisol, EDI-2 **Exclusion**: All: IQ less than 85, current inflammatory, neurological or metabolic illness, chronic bowel diseases, cancer, anemia, pregnancy, breastfeeding, treatment with cortisone, psychotropic medications within the past 6 month AN-Rec: BMI < 18.5 (if older than 18 years) or a BMI < 10th BMI percentile last 3 months prior to study, binged, purged or engaged in significant restrictive eating patterns CO: psychiatric illness, organic brain syndrome, schizophrenia, substance dependence, bipolar illness, bulimia nervosa, binge-eating disorder	Reduced POMC-related peptides in CSF of 10 AN cases (PMID: 2823041) → mechanistic hypothesis of altered central nervous appetite regulation
Ehrlich (2012)	AN: 40 AN-Rec: 21 CO: 54	100% 100% 100%	17.88 (3.2) 19.25 (3.7) 17.10 (2.3)	DSM-IV	n.a.	Whole blood - uncorrected - proxy tissue - discussed	*POMC*	↔ ↔			**Confounds**: Age, duration of illness, leptin, BMI, smoking **Exclusion**: All: IQ < 85, current inflammatory, neurological or metabolic illness, chronic bowel diseases, cancer, anemia, pregnancy, breastfeeding, treatment with cortisone, and use of psychotropic medications within the past 6 months Patients: organic brain syndrome, schizophrenia, substance dependence, bipolar disorder, bulimia nervosa, binge-eating disorder	Follow-up study to Ehrlich (2010) to correct for possible confounds
Pjetri (2013)	AN: 45 CO: 45	n.a. n.a.	16–60 n.a.	DSM-IV-TR	n.a.	Whole blood - uncorrected - proxy tissue - discussed	*DRD2* *LEP* *BDNF* *SLC6A4*	↔ ↔ ↔ ↔			**Confounds**: BMI	No hypothesis, only prior epigenetic studies and candidate gene relevance to neurotransmitter and body weight regulation systems
Steiger (2013)	BN: 64 CO: 32	100% 100%	26.1 (6.6) 23.7 (5.7)	DSM-IV-TR	52.4%	Whole blood - uncorrected - proxy tissue - discussed	*GR*		↔		**Confounds**: Borderline personality disorder, suicidality, childhood abuse, binge eating and vomiting frequency, BMI, medication **Exclusion**: CO: Current or past clinical eating disorder symptoms per EDE-Q, childhood abuse, borderline personality disorder	Less suppression in a dexamethasone suppression test of 60 women affected by bulimia spectrum disorder (PMID. 22575215) → mechanistic hypothesis of glucocorticoid system alterations
Groleau (2014)	BN: 52 CO: 19	100% 100%	24.7 (5.7) 23.7 (4.6)	DSM-IV-TR	67.3%	Whole blood - uncorrected - proxy tissue - discussed	*DRD2*		↔		**Confounds**: Borderline personality disorder, physical and sexual childhood abuse, bingeing and vomiting frequency, BMI, medication **Exclusion**: CO: Current or past clinical eating disorder symptoms per EDE-Q, childhood maltreatment	No hypothesis, only prior epigenetic studies

Table 1 (continued)

Author (Year)	Sample				Medicated	Tissue/cell type - Correction - Suitability - Limitation	Methylation results				Assessed confounds and exclusion criteria	Biological hypothesis (PMID) → mechanistic or potential biomarker study
	N	Female	Age (SD/range) [years]	Diagnoses			Candidate genes	AN	BN	BED		
Kim (2014)	AN: 15 CO: 36	100% 100%	24.7 (10.7) 22.1 (2.2)	DSM-IV	0%	Buccal cells - uncorrected - proxy tissue - discussed	*OXTR*	↑			**Confounds**: Age, BMI, EDE-Q global score, AQ total score, BDI, STAI-S, STAI-T **Exclusion**: All: smoking, non-heterosexual, parous, medications, including contraceptives, history of psychiatric illness, < 18 years old Patients: active substance use disorder, psychotic disorder (schizophrenia, schizoaffective, psychosis not otherwise specified), autism, Asperger's syndrome	Derangement of the oxytocin system in AN cases (PMID: 24115458) → mechanistic hypothesis of oxytocin system alterations
Saffrey (2014)	AN: 10 CO: 10	100% 100%	21.5 (10.16) 23.1 (9.45)	n.a.	n.a.	Buccal cells - uncorrected - proxy tissue - discussed	*IGF2*	↔			**Confounds**: None **Exclusion**: None	No hypothesis, only prior epigenetic studies
Thaler (2014)	BN: 64 CO: 32	100% 100%	26.1 (6.6) 23.7 (5.7)	DSM-5	52.4%	Lymphocytes - not necessary - proxy tissue - discussed	*BDNF*		↑		**Confounds**: Borderline personality disorder, physical or sexual childhood abuse **Exclusion**: CO: Childhood abuse	Decreased serum BDNF in 22 AN cases (PMID: 15385700) Decreased serum BDNF in 18 BN cases and 12 AN cases (PMID: 12915293) → mechanistic hypothesis that alterations in BDNF methylation are related to early-life adversities
Veldic (2017) Jia (2017)	BED/BN: 30 CO: 32	76.7% 56.3%	45.2 (14.8) 37.4 (13.4)	DSM-IV-TR	60%	Blood - uncorrected - proxy tissue - not mentioned	*SLC1A2*		↓	↓	**Confounds:** BMI, age, sex, cumulative illness rating scale, rapid cycling, increased severity, mixed episodes, cycle acceleration, psychosis, anxiety disorder, early onset (< 20 years), atypical antipsychotics, lithium, valproate, and lamotrigine, current alcohol use (≥2x per month), current smoker status, and lifetime history of smoking (≥100 cigarettes) **Exclusion**: CO: History of serious mental illness, alcohol abuse or dependence, nicotine dependence	In a sample of 68 bipolar disorder patients comorbid BED was prevalent after controlling for obesity (PMID: 23742827) Antagonism of the glutamatergic system decreased food intake in baboons (PMID: 18573641) → mechanistic hypothesis of glutamatergic neurotransmission influencing food intake

Author (Year)	Sample				Medicated	Tissue/cell type - Correction - Suitability - Limitation	Methylation results				Assessed confounds and exclusion criteria	Biological hypothesis (PMID) → mechanistic or potential biomarker study
	N	Female	Age (SD/Q1, Q2) [years]	Diagnoses			EWAS	AN	BN	BED		
Booij (2015)	AN: 29 CO: 15	100% 100%	22.7 (5.9) 24.2 (5.8)	DSM-5	73%	Lymphocytes - not necessary - proxy tissue - uncritically discussed		14 CpG			**Confounds**: None **Exclusion**: None	No hypothesis, only prior epigenetic studies

Table 1 (continued)

Author (Year)	Sample				Medicated	Tissue/cell type - Correction - Suitability - Limitation	Methylation results				Assessed confounds and exclusion criteria	Biological hypothesis (PMID) → mechanistic or potential biomarker study
	N	Female	Age (SD/Q1, Q2) [years]	Diagnoses			EWAS	AN	BN	BED		
Kesselmeier (2016)	AN: 47 CT: 47 CO: 100	100% 100% 100%	16 (14, 17) 22 (21, 23) 60 (54, 69)	DSM-IV	n.a.	Whole blood - FastLMM-EWASher corrected (PMID: 24464286) and RefFree- EWAS corrected (PMID: 24451622) - proxy tissue - mentioned	AN vs CT AN vs CO	51 CpG 81 CpG			**Confounds**: None **Exclusion**: CT: somatic disorders, ≤10 cigarettes per day, AN, BN, cognitive restraint (Three-Factor Eating Questionnaire), weight history (higher weight than same-aged individuals at ages 10, 15 and/or 18) CO: none	No hypothesis, only prior epigenetic studies
Ramoz (2017)	AN: 18 AN-Rec: 18	100% 100%	n.a.	n.a.	n.a.	n.a.	n.s.	↔			**Confounds**: n.a. **Exclusion**: n.a.	n.a.

↑ = increased methylation level, ↔ = unchanged methylation level, ↓ = decreased methylation level, *AN* anorexia nervosa, *AN-Rec* recovered from anorexia nervosa, *ANP/NPPA* natriuretic peptide A, *AQ* Autism Spectrum Quotient, *BDI* Beck Depression Inventory, *BDNF* brain derived neurotrophic factor, *BED* binge-eating disorder, *BMI* body mass index, *BN* bulimia nervosa, *CDI* Children's Depression Inventory, *CNR1/CB1* cannabinoid receptor 1, *CNR2/CB2* cannabinoid receptor 2, *CO* controls, *CpG* CpG sites, *CSF* cerebrospinal fluid, *CT* constitutionally thin, *DAT/SLC6A3* dopamine transporter, *DRD2* dopamine receptor D2, *DRD4* dopamine receptor D4, *DSM* Diagnostic and Statistical Manual of Mental Disorders, *EDE-Q* Eating Disorder Examination Questionnaire, *EDI* Eating Disorders Inventory, *EWAS* epigenome-wide association study, *GR/NR3C1* glucocorticoid receptor, *HERP/HERPUD1* homocysteine inducible ER protein with ubiquitin like domain 1, *IGF2* insulin like growth factor 2, *IQ* intelligence quotient, *LEP* leptin, *n.a.* not available, *N* number, *NR3C1/GR* nuclear receptor subfamily 3 group C member 1, *n.s.* not significant, *OXTR* oxytocin receptor, *PMID PubMed-Indexed for MEDLINE*, *POMC* proopiomelanocortin, *Q1* quartile 1, *Q3* quartile 3, *SD* standard deviation, *SLC1A2* solute carrier family 1 member 2, *SLC6A3/DAT* solute carrier family 6 member 3, *SLC6A4* solute carrier family 6 member 4, *SNCA* synuclein alpha, *STAI* Spielberger State and the Trait Anxiety Inventory

Canada [48–51]. Most studies investigated surrogate tissues with regard to their biological hypotheses, including whole blood, lymphocytes, or buccal cells instead of brain or metabolic tissue, and did not correct for heterogeneity of these tissues. Ten studies discussed the limitations of using surrogate tissues in their articles, two mentioned the issue, and four did not elaborate on this limitation (Table 1).

Global DNA methylation levels

Four studies investigated global DNA methylation differences in eating disorders. All studies primarily focused on AN [45, 51–53], with one study also investigating BN [45]. Two studies reported global hypomethylation in individuals with AN [45, 53], one study reported global hypermethylation in AN [51], and one reported no difference in global DNA methylation levels between AN cases and controls [52]. Patients suffering from BN showed no difference in their global DNA methylation levels compared with controls [45]. Overall the quality of evidence resulting from these studies was very low with inconsistent findings of opposite effects (Supplementary Table 1).

Candidate gene studies

Candidate gene studies are hypothesis-driven and investigate DNA methylation in the vicinity of selected genes. These candidate genes are selected based on prior knowledge, for example, following differences in protein levels measured in clinical studies assessing patients with AN or BN. Overall, 13 studies have been published profiling DNA methylation in candidate gene regions in the context of eating disorders, twelve of which focus on AN (n = 9) and BN (n = 6). These twelve studies investigated genes relating to synaptic transmission [45], endoplasmatic reticulum stress response [45], growth hormone signaling [52], fluid balance [42], the cannabinoid system [43], dopamine transmission [44, 50, 54], stress response [46, 48], appetite regulation [46, 49, 54], serotonin transmission [54], and oxytocin [55]. One methylomic study of candidate genes in BED has been reported [56, 57]. The study investigated promoter methylation of *SLC1A2*, a gene involved in glutamate clearance, in bipolar disorder. The authors found decreased DNA methylation in bipolar disorder patients who also suffered from BED, compared to those who were only affected by bipolar disorder. However, their sample of patients reporting binge-eating behavior seemed to comprise BN and BED cases, rendering the interpretation of the results ambiguous [56, 57]. All candidate gene studies of eating disorders are described in detail in Table 1. The overall quality of the evidence was very low with small

Table 2 Epigenome-wide association study (EWAS) follow-on investigations

Author (Year)	Multiple testing correction	Variability filters	Follow-up on hits	Validation on different platform	Function of identified sites
Booij (2015)	Bonferroni and False Discovery Rate (FDR)	Probes needed to have a standard deviation of at least 0.05 (5% deviation in methylation)	Pathway analysis (Ingenuity Pathway Analysis)	No	Histone acetylation and RNA modification, cholesterol storage and lipid transport, and dopamine and glutamate signaling
Kesselmeier (2016)	None	Average beta value across all samples between 0.1 and 0.9	Validation of direction of effect in monozygotic twins discordant for AN	No	n.a.
Ramoz (2017)	n.a.	n.a.	Pathway analysis	n.a.	n.a.

n.a. not available, *RNA* ribonucleic acid, *AN* anorexia nervosa

sample sizes never exceeding ~120 participants (Supplementary Table 1).

Epigenome-wide association studies (EWAS)

Three EWAS investigated genome-wide DNA methylation profiles in AN using the Illumina Infinium® HumanMethylation450 BeadChip. No genome-wide studies of DNA methylation have been published on other eating disorders. Booij et al [51] reported 14 differentially methylated CpG sites comparing 29 AN patients with 15 normal-weight controls. These 14 hypermethylated CpG sites were annotated to 11 genes (*PRDM16, HDAC4, TNXB, FTSJD2, PXDNL, DLGAP2, FAM83A, NR1H3, DDX10, ARHGAP1, PIWIL1*) [51]. Kesselmeier et al. [30] reported 51 differentially methylated CpG sites when comparing 22 AN cases with 24 lean individuals and 81 CpG sites when comparing AN cases with 30 individuals from a general population sample. They also showed that 54 of the 81 sites exhibited directionally consistent differential DNA methylation differences in a comparison of twins discordant for AN assessed by a binomial sign test (Table 2). Although the authors report a replication of hypermethylation previously reported at a CpG site annotated to *TNXB* [30, 51], the significance level for this replication was only suggestive. In this study, controls recruited from the population were on average significantly older than the AN patients potentially confounding the results as methylation patterns are age-dependent [25, 30]. In a conference presentation, Ramoz et al [41] conducted the only longitudinal investigation of 36 acutely ill AN patients of whom half remitted after one year. However, the statistical analysis performed was cross-sectional. No significant differences in DNA methylation emerged between remitted AN patients and those patients who were still ill after a follow-up period of 1 year. However, the study did not include a control group [41]. Two of the three EWAS were followed up by pathway analyses (Table 2) [41, 51].

Discussion

The current research on epigenetics in eating disorders is limited and not yet sufficiently mature to draw sound conclusions with most evidence of the reviewed studies being of very low quality. To date, epigenetic research in eating disorders has, to our knowledge, focused exclusively on DNA methylation, using three different approaches to investigate disease-associated methylomic variation. First, early DNA methylation studies measured global methylation levels in eating disorder cases comparing them with methylation levels in healthy controls. Second, DNA methylation at selected candidate genes has been assessed. Third, genome-wide approaches are applied in the investigation of epigenetic alterations in EWAS. In general, studies were cross-sectional and primarily focused on females. Most studies were conducted on surrogate tissue and presented varying degrees of acknowledgement and discussion of the limitations of using surrogate tissues in epigenetic epidemiology.

Overall, global methylation study results were inconclusive and inconsistent and did not reveal a clear and replicable global DNA methylation pattern in either AN or BN. All four studies were small, with the largest study profiling 32 AN cases and 24 BN cases, substantially limiting the power to detect effects. More generally, global levels of DNA methylation may not be of much relevance to epigenetic epidemiology, as they fail to provide information on region-specific DNA methylation, and lack the specificity to associate the dysregulation of biological pathways with the occurrence of a disease [58]. Even within the framework of global DNA methylation studies, the methods employed in these four studies limit the examination of DNA methylation to either promoter regions (for

the approaches based on methylation sensitive restriction enzymes) or LINE1 elements [52], overlooking other parts of the genome.

Across candidate gene studies, no clear differentially methylated candidate genes for AN, for BN, or for BED were robustly identified. Most candidate regions were only profiled once, and results of repeatedly measured genes involved in dopamine signaling did not replicate across studies [44, 50, 54], showing no clear eating disorder-associated methylomic variation across the selected candidate genes. In addition to non-replication, these studies were limited by small sample sizes rendering them imprecise: most of the study populations included on average only 30 cases with two studies including 64 cases [49, 50]. Furthermore subjects occasionally comprised a mixture of acutely ill and recovered patients [55] or a mixture of different eating disorders [56, 57] introducing heterogeneity. This is particularly concerning as dietary changes, weight changes, and accompanied alterations of hormonal concentrations during the recovery process can have a major effect on epigenetic profiles in individuals with eating disorders. Further possible confounders are discussed below. In epigenetics, as in genetics, a general drawback of a candidate gene studies is their hypothesis-driven design. Specific genes are selected for investigation based on prior knowledge, narrowing the investigation to only a very limited part of a large system and failing to attend to the majority of other genomic regions.

In general, hypothesis-free approaches that explore the whole genome are the gold standard in genetic research. Genome-wide approaches are applied in the investigation of common genetic variation (i.e., single nucleotide polymorphisms, SNPs) in genome-wide association studies (GWAS) as well as in the examination of epigenetic alterations in EWAS. EWAS examining CpG sites at a genome-wide level have identified multiple AN-associated differentially methylated sites, replicating a differentially methylated position at *TNXB* in one independent study [51]. However, the hypermethylation at this CpG site annotated to *TNXB* only reached suggestive significance in the replication attempt [30], failing to survive stringent correction for multiple comparisons. A false positive finding, therefore, cannot be ruled out.

Statistically, EWAS share similarities with GWAS in that site-specific associations with a phenotype across a large number of genomic loci are conducted. These statistical properties limited the findings in EWAS investigating eating disorders: First, the reported samples never included more than 29 cases of AN which is far too small to robustly detect patterns of differential methylation at a genome-wide scale, i.e., when conducting over 450,000 statistical tests [59], leading to imprecise estimates of the effects. Second, multiple testing correction was not always performed stringently, e.g., when "suggestive" significant results were reported or examined sites were filtered before or after analysis based on methylation variability.

As such, many of the EWAS included above were labeled as pilot studies by the authors and provide motivation for further investigation, and are a springboard to launch full-scale projects with larger sample sizes and careful study design, data collection, and analysis. Future studies will also require replication in independent samples and should adhere to stringent methodological criteria, including multiple testing correction, no subjective filtering of CpG sites, and controlling for confounding factors.

Future directions

Sample size

One of the primary goals of future epigenetic investigations of eating disorders should be to increase sample sizes by international collaborations to improve the power to detect effects, even when effect sizes are small. Recent epigenetic studies of other psychiatric disorders and environmental exposures have examined epigenetic differences in samples comprising thousands of participants and notably, replicated successes have been documented for a number of exposures and diseases including tobacco smoking [24], C-reactive protein levels in serum blood [60], and Alzheimer's disease [16, 17]. While several large consortium efforts have led to advances in characterizing baseline human tissue epigenomes [10, 61, 62], this is rarely extended to the realm of epigenetic epidemiology in complex diseases. Unique challenges do exist in conducting large-scale collaborative epigenetic studies. Combining raw data (i.e., mega-analytic approaches) in epigenetics is problematic because technical variation in the data stemming from different laboratories and procedures (i.e., batch effects) has substantial impact on overall epigenomic profiles and can be insufficiently controlled for by post-hoc statistical or computational approaches [63, 64]. Nonetheless, approaches in which each site generates a sufficiently large sample under nearly identical conditions that can later be meta-analyzed are feasible [27]. Alternatively, consistent sampling at different study sites including careful preanalytic sample collection and processing followed by analysis in a central laboratory could prevent many of the aforementioned technical issues. However, this approach is only feasible if all study sites meticulously follow the same protocol regarding tissue sampling, sample handling, and phenotyping of participants to control for possible confounders

across study sites. This kind of pooling approach tends to be complicated by challenges associated with sample storage, transportation, and loss.

Statistical methods

As with any genome-wide investigation, the large number of tests performed requires special considerations for statistical analysis. Most importantly, it is essential to correct for the number of tests performed. The latest generation of DNA methylation arrays can simultaneously quantify epigenetic profiles at up to 850.000 CpG sites. An EWAS then tests for associations between a phenotype of interest and DNA methylation at each of these sites. Each of the 850.000 tests has a small probability of reporting a false positive association (usually 5%). In order to keep the probability of making any false positive discovery below this probability threshold, the individual *P* value thresholds for each test need to be adjusted, resulting in a genome- or array-wide significance threshold. This correction for multiple testing can be achieved by common methods such as Bonferroni correction (dividing the *P* value threshold by the number of tests conducted) or a false discovery rate correction [65, 66].

Tissue specificity

Given the prominent role epigenetic mechanisms play in cellular differentiation, genome-wide epigenetic profiles tend to differ substantially between different tissues and cell-types, matching the differences in function (e.g., fat storage in adipose tissue vs. synaptic transmission performed by neurons). Different cellular functions require particular sets of proteins acting in concert (i.e., pathways) and epigenetic mechanisms control which genes are active in which cell-type and tissue-context. Interestingly, epigenetic profiles can distinguish functionally different brain regions [67] and cell-types [68, 69]. Is disease-associated epigenetic dysregulation tissue-specific? For example, are epigenetic correlates of psychiatric diseases restricted to the brain? In some disorders, including AN, it is less straightforward to pinpoint the affected tissue of interest. AN is characterized by both psychiatric and metabolic features [6]. Therefore, one would ideally investigate epigenetic profiles in both brain tissue and metabolic tissues (e.g., adipose tissue, pancreas, liver, stomach, and the intestine). The investigation of brain in particular, however, poses considerable challenges and is typically only possible in postmortem samples, which introduces additional complications for epigenetic studies (e.g., time of death, cause of death, etc.). Nonetheless, carefully designed, ethical discussions of organ donations with patients and families are worthy of consideration.

Surrogate tissues

Although investigation of epigenetic profiles in the disease-affected tissue is the gold standard in epigenetic studies, it is also valuable to examine epigenetics in surrogate peripheral tissues, including whole blood, epithelial cells, and saliva. First, while epigenetic profiles are highly tissue-specific and profiles observed in peripheral tissues are not generally representative of epigenetic variation in brain, specific genomic regions manifest high levels of epigenetic covariation [67, 70, 71]. For example, an existing online platform allows for the profiling of DNA methylation covariation between whole blood and multiple brain regions (//epigenetics.essex.ac.uk/bloodbrain/). Second, while results emerging from epigenetic studies from peripheral samples might not necessarily reflect the epigenetic changes in disorder-relevant tissues, they can still be used as potential biomarkers, and are collected more readily and less invasively than the affected tissue itself. Importantly, when analyzing whole blood epigenetic profiles, the blood cell-type composition also needs to be assessed. Blood is a heterogeneous organ comprised of distinct cell types, fulfilling specific tasks, such as oxygen transport, immune function, and nutrient distribution. Because blood composition in patients suffering from eating disorders differs from controls [30], it is imperative to control for these differences in cell-type composition. If unaccounted for, epigenetic differences identified in an association scan could be related purely to differences in cellular composition rather than epigenetic dysregulation directly linked to disease etiology and progression. Where blood cell counts are not available, validated estimators of subcell proportions based on large reference panels can be used; i.e., cell-type proportions can accurately be estimated using microarray-based DNA methylation data. This also applies to other cell-types, and estimators based on DNA methylation array data have been previously reported for whole brain, buccal swabs, and saliva samples. These estimators require array-wide DNA methylation profiles and are therefore not applicable in candidate gene studies [72].

Genome-wide integrated epigenetic studies

Many of the studies reviewed here use targeted sequencing approaches, which only allow the investigation of DNA methylation in limited genomic regions and ignore information from the rest of the genome. This may increase the chances for false positive reports via a

publication bias of positive findings. Genome-wide technologies are less prone to this phenomenon and allow for the verification of previously reported differentially methylated sites. While only whole genome bisulfite sequencing allows full coverage of the entire genome, array-based approaches like Illumina's EPIC array, allow widespread coverage of CpG sites in most genomic regions and can be a more cost-effective solution.

All epigenetic studies of eating disorders published to date focused on DNA methylation only. A host of other sources of regulatory variation including other DNA modifications, histone modifications, and non-coding RNAs should also be investigated. Furthermore, to better interpret the role of epigenetic modifications in disease, it is important to understand their interactions with the genetic sequence itself. Integrated analyses incorporating genotypic, epigenetic, transcriptomic, and detailed environmental data are beginning to emerge, elucidating the role of disease-associated epigenetic dysregulation in specific genetic and environmental contexts. Increasingly detailed maps of genetic and (multi)epigenetic profiles in health and disease will be essential to improve our understanding of the molecular biological pathways implicated in complex disease.

Eating disorder-specific considerations

In addition to these general recommendations for improving epigenetic research in disease epidemiology, there are also a number of important eating disorder-specific complexities to be considered.

Eating disorder-specific confounders

Because epigenetic modifications are dynamic and can be altered by environmental influences, epigenetic association studies are subject to a wide range of confounders. Confounding in EWAS is comparable to classic observational epidemiological studies and ideally these confounders are addressed in the study design in such a way that they can be controlled for in the statistical analyses. For example, age, sex, diet, micronutrients, medication, dietary supplements, hormones, smoking, and alcohol consumption can interact with an individual's epigenetic profile, obfuscating EWAS analyses (Fig. 2).

A large body of evidence confirms that diet composition can have an effect on an individual's epigenetic profile [73–77]. Eating and compensatory behaviors can include binge eating and purging behaviors, abuse of diet medication, laxatives, and diuretics altering fluid balance. It is important to record their typical use, as well as the frequencies and recency of use and, ideally, obtaining blood levels of diet medications when possible. Both indicated and off-label prescribed antidepressants, anticonvulsants, and atypical antipsychotics are used to control accompanying symptoms observed in patients suffering from eating disorders [78]. Dosage and intake should be included in the analysis, ideally, blood levels should be measured, and statistical analyses corrected for. This strategy should also be followed for supplements, such as vitamins and micronutrients, and hormones as patients with eating disorders often show hormonal alterations, such as high cortisol and low sex hormones [79, 80]. These types of hormones are direct ligands to so-called promoters, enhancers, and silencers and, therefore, influence gene expression and protein levels directly. Weight differences between cases and controls should be accounted for; however, if substantial between group differences exist between cases and controls, disease and weight-associated epigenetic variation will remain convoluted. One option in addressing this issue is using a matched weight control group, potentially in addition to normal weight controls, in order to tease apart epigenetic correlates of eating disorder versus altered weight phenotypes. However, this approach may be limited because constitutionally thin individuals rarely have a BMI as low as patients suffering from severe AN. Environmental toxins, such as smoking and alcohol, can have a profound impact on the epigenome. For example, prevalence differences in smoking between cases and controls have been shown to confound the association between DNA methylation and schizophrenia [14].

As with every observational study design, the causal attribution of epigenetic associations in eating disorders is extremely difficult. The epigenetic dysregulation could potentially have causally contributed to the disease or have arisen as a consequence of the disease, its symptoms or even treatments, such as medication; [81] or, in a third scenario, there could be a third factor driving both the disease and the epigenetic alteration, which have no direct link between one another. One important approach to addressing causality is to consider temporal factors [26, 27]. A variety of chronologically variable factors should be taken into account, such as age of disorder onset, duration of illness, onset of menstrual disturbances, and duration of amenorrhea (in women). Longitudinal sampling and within-subject comparisons can help differentiate between sequelae of starvation or overeating and epigenetic factors that contribute to the liability to develop an eating disorder. In addition to this, methods using genetic variants as instrumental variables can improve causal inference. In epigenetic epidemiology, Mendelian randomization is of particular importance, exploiting genetic influences on DNA methylation (mQTLs) to understand whether phenotypic associations of DNA methylation are indeed causal [82].

Conclusion

Epigenetic research in eating disorders is still in its infancy, but initial results from pilot studies encourage further and larger-scale investigation. Much like progress in genomics, international collaborations are required to amass adequately powered sample sizes to draw credible conclusions from epigenetic investigations. Even more importantly, careful study design is of vital importance in epigenetics and can aid in avoiding potential pitfalls. Robust, replicable results from carefully designed studies have the potential to uncover the molecular biological processes involved in disease onset and progression, they may help characterize gene regulatory effects of non-coding genetic variation, and, hopefully, give indications into disease-relevant biological pathways which could be addressed by therapeutic interventions. Clearly a considerable amount of functional work is required in follow-up of epigenetic association studies to better understand the gene regulatory, cellular, and organismal outcomes of epigenetic variation and derive potential translational implications and therapeutic avenues. Even non-functional disease-associated epigenetic variation from peripheral tissue sources could, however, have useful implications as biomarkers for risk and prognosis assessment and for use in early diagnosis.

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Compliance with ethical standards

Conflict of interest Dr. Bulik reports: Shire (grant recipient, Scientific Advisory Board member) and Pearson and Walker (author, royalty recipient) (unrelated to the content of this manuscript). Dr. Breen has received grant funding from and served as a consultant to Eli Lilly and has received honoraria from Illumina (all unrelated to the content of this manuscript). The remaining authors declare that they have no conflict of interest.

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Appendix 2 Body composition in anorexia nervosa: meta-analysis and meta-regression of cross-sectional and longitudinal studies

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Online Supporting Information

Secondary outcomes: bone mineral measures

2.1) Results

Secondary outcomes: metabolites and hormones

2.2) Results

Meta-analyses: forest plots

2.3) Meta-analyses of study sample characteristics comparing anorexia nervosa patients with healthy controls

2.4) Q value plot of meta-analyses uncapped

2.5) Cross-sectional meta-analyses of studies comparing acutely-ill/pre-treatment anorexia nervosa patients with healthy controls

2.6) Cross-sectional meta-analyses of studies comparing post-treatment anorexia nervosa patients with healthy controls

2.7) Longitudinal meta-analyses of studies comparing anorexia nervosa patients pre- and post-treatment

2.8) Cross-sectional meta-analyses of studies comparing weight-recovered anorexia nervosa patients with healthy controls

Adjustment for small study effects

2.9) Copas selection models

2.1 Results: Secondary outcomes: detailed bone mineral measures

Before treatment, anorexia nervosa (AN) patients exhibited lower bone mineral density in every region compared to controls: lumbar spine (-0.14 g/cm^2, CI 95%: -0.18, -0.10, Q = 2.32 x 10^{-12}), femoral neck (-0.14 g/cm^2, CI 95%: -0.18, -0.09, Q = 1.93 x 10^{-9}), and hip (-0.13 g/cm^2, CI 95%: -0.15, -0.11, Q = 6.20 x 10^{-45}) that persisted at the lumbar spine (-0.08 g/cm^2, CI 95%: -0.12, -0.04, Q = 1.63 x 10^{-4}) and femoral neck (-0.10 g/cm^2, CI 95%: -0.15, -0.04, Q = 0.001) even after weight recovery. Again, the post-treatment estimates have limited validity as they were based on only two studies with 31 AN cases and insufficient follow-up duration. The meta-regressions showed that pre-treatment bone mineral densities were associated with duration of illness (hip; $\beta_{metareg}$ = -0.001 months, p = 0.05; lumbar spine; $\beta_{metareg}$ = -0.001 months, p = 0.02), age of AN cases (hip; $\beta_{metareg}$ = -0.005 years, p = 0.03; lumbar spine; $\beta_{metareg}$ = -0.01 years, p = 0.003), and the differences in fat mass (femoral neck; $\beta_{metareg}$ = 0.01 kg, p = 0.02; lumbar spine; $\beta_{metareg}$ = 0.01 kg, p = 0.04) and body fat percentage (lumbar spine; $\beta_{metareg}$ = 0.01, p = 0.001) between cases and controls (Supporting Information Table S4). Cases and controls in our meta-analyses were age- and height-matched (Supporting Information Figure S2 & S6), therefore, these variables cannot be associated with the mean difference between cases and controls.

2.2 Results: Secondary outcomes: metabolites and hormones

Glucose homeostasis, gastrointestinal hormone, and adipokines

Pretreatment fasting glucose (-7.01 mg/dL, CI 95%: -9.61; -4.40, $p_{Copas} < 1.00 \times 10^{-4}$) after adjustment for publication bias and insulin (-19.23 pmol/L, CI 95%: -31.68, -6.77, $Q = 0.005$) were lower in AN than controls, but reached concentrations of healthy controls after treatment increasing by 9.51 mg/dL (CI 95%: 2.68, 16.35, $Q = 0.01$) and 15.92 pmol/L (CI 95%: 1.89, 29.95, $Q = 0.05$) during treatment. Neither fasting glucose nor fasting insulin were associated with body composition in AN patients before treatment (Supporting Information Table S4). Ghrelin was 149.2 pmol/L (CI 95%: 54.59, 243.81, $Q = 0.004$) higher than controls before treatment, decreased by 107.76 pmol/L (CI 95%: -161.47, -54.05, $Q = 2.06 \times 10^{-4}$) during treatment, and reached comparable concentrations of healthy controls after treatment. No differences in adiponectin were observed between pre-treatment comparing AN cases and healthy controls. After adjustment for publication bias, pre-treatment leptin was 7.20 ng/mL (CI 95%: -8.44, -5.96, $p_{Copas} < 1.00 \times 10^{-4}$) lower than control values and associated with the difference in fat mass between AN patients and healthy controls ($\beta = 0.80$, $p = 0.003$) as indicated by meta-regression (Supporting Information Table S4). Leptin increased by 2.83 ng/mL (CI 95%: 1.22, 4.44, $Q = 0.001$) across treatment and showed a mean difference of -3.91 ng/mL (CI 95%: -7.37, -0.45, $Q = 0.05$) after treatment compared to controls. In weight-recovered individuals with AN, leptin concentrations were within the range of healthy controls. Although our analyses were meta-analytic, sample sizes of most comparisons regarding secondary outcomes were still small (Table 1).

Thyroid, adrenal, growth, and sex hormones

On average and before treatment, AN patients presented with lower fT_3 (-1.32 pmol/L, CI 95%: -1.64, -1.00, $Q = 6.85 \times 10^{-15}$) and fT_4 (-2.60 pmol/L, CI 95%: -3.26, -1.93, $Q = 1.23 \times 10^{-13}$), but their mean TSH did not differ significantly from healthy controls. Pre-treatment fT_3 was associated with body fat percentage in AN patients ($\beta = -0.14$, $p = 0.05$) and with the difference in fat mass between AN patients and controls ($\beta = 0.14$, $p = 0.001$) as indicated by meta-regression (Supporting Information Table S4). During treatment, fT_3 increased by 0.80 pmol/L (CI 95%: 0.39, 1.21, $Q = 3.08 \times 10^{-4}$). However, post-treatment concentrations still differed by 0.91 pmol/L (CI 95%: -1.36, -0.47, $Q = 1.40 \times 10^{-4}$) between AN cases and controls. This finding was limited by an extremely small sample size ($n_{AN} = 33$).

In comparison with controls, the mean pre-treatment cortisol was 131.92 nmol/L (CI 95%: 86.26, 177.58, $Q = 5.46 \times 10^{-8}$) higher in AN patients and showed an association with fat mass ($\beta = 87.13$, $p = 0.04$) as indicated by meta-regression. Estradiol was significantly lower (-40.83 pg/mL, CI 95%: -55.43, -26.23, $Q = 1.49 \times 10^{-7}$) in AN patients and associated with fat-free mass ($\beta = -9.71$, $p = 2.56 \times 10^{-11}$) and duration of illness ($\beta = 0.54$, $p = 0.009$) as indicated by meta-regression. Estradiol was also associated with the difference in fat-free mass ($\beta = 8.69$, $p = 0.02$) between AN patients and healthy controls (Supporting Information Table S4). In contrast, testosterone concentrations showed no difference between cases and controls. IGF-1 in AN cases was significantly lower by 95.86 µg/L (CI 95%: -117.93, -73.8, $Q = 1.22 \times 10^{-16}$) than healthy controls before treatment. IGF-1 was positively associated with age ($\beta = 14.95$, $p = 7.31 \times 10^{-7}$) and the difference in body fat percentage between cases and controls ($\beta = 4.57$, $p = 0.04$) as indicated by meta-regression (Supporting Information Table S4).

The number of longitudinal studies reporting detailed body composition in combination with metabolites and hormones was too low to perform meta-regressions for our secondary outcome the biochemical measures post-treatment and after weight recovery, indicating that the published literature is insufficient to draw conclusions at the current stage.

Methodological moderators

Furthermore, femoral neck bone mineral density ($\beta_{Outpatient}$ = -0.12, p = 7.65 x 10^{-4}), leptin ($\beta_{Outpatient}$ = 4.65, p = 0.04), fasting glucose ($\beta_{Outpatient}$ = -10.52, p = 0.01), estradiol ($\beta_{Outpatient}$ = -29.23, p = 1.01 x 10^{-11}), and IGF-1 ($\beta_{Outpatient}$ = -40.22, p = 0.004) significantly differed between inpatients and outpatients. Ghrelin concentrations (β_{Serum} = -173.11, p = 6.41 x 10^{-7}) were the only blood parameter associated with blood sample type, indicating that concentrations of all other blood parameters were comparable between serum and plasma.

2.3 Meta-analyses of study sample characteristics comparing anorexia nervosa patients with healthy controls

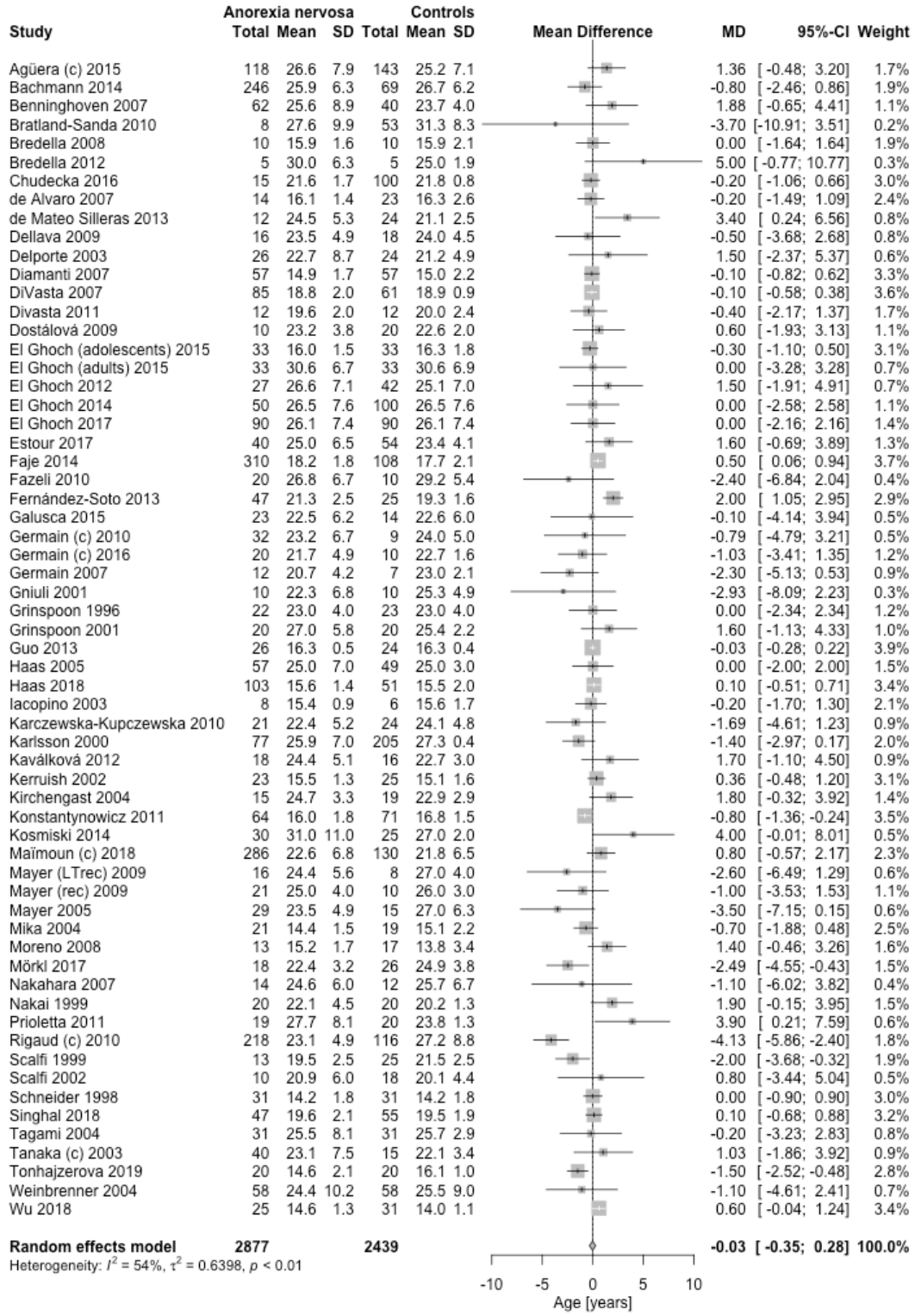

Figure S1. Cross-sectional meta-analysis of studies reporting mean age in anorexia nervosa patients compared with healthy controls. Sixty-two samples had the appropriate data for the meta-analysis with 2,877 AN cases and 2439 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.03 years; 95% CI: -

0.35, 0.28; *P* = 0.83). C, subtype-combined sample; LTrec, long term weight-recovered; rec, recovered.

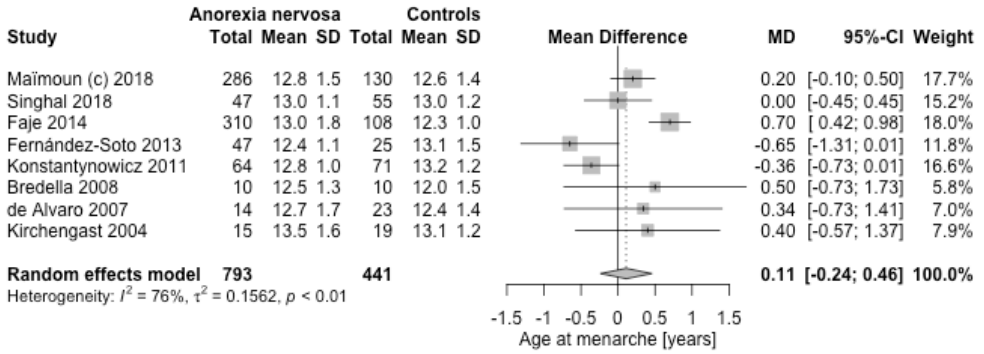

Figure S2. Cross-sectional meta-analysis of studies reporting age at menarche in female anorexia nervosa patients compared with healthy controls. Eight samples had the appropriate data for the meta-analysis with 793 AN cases and 441 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 0.11 years; 95% CI: -0.24, -0.46; *P* = 0.54) with the mean differences ranging from -0.65 years to 0.70 years. Heterogeneity between studies was statistically significant (τ^2 = 0.16; *P* < 0.01; I^2 = 76%). C, subtype-combined sample.

2.4 Q value plot of meta-analyses uncapped

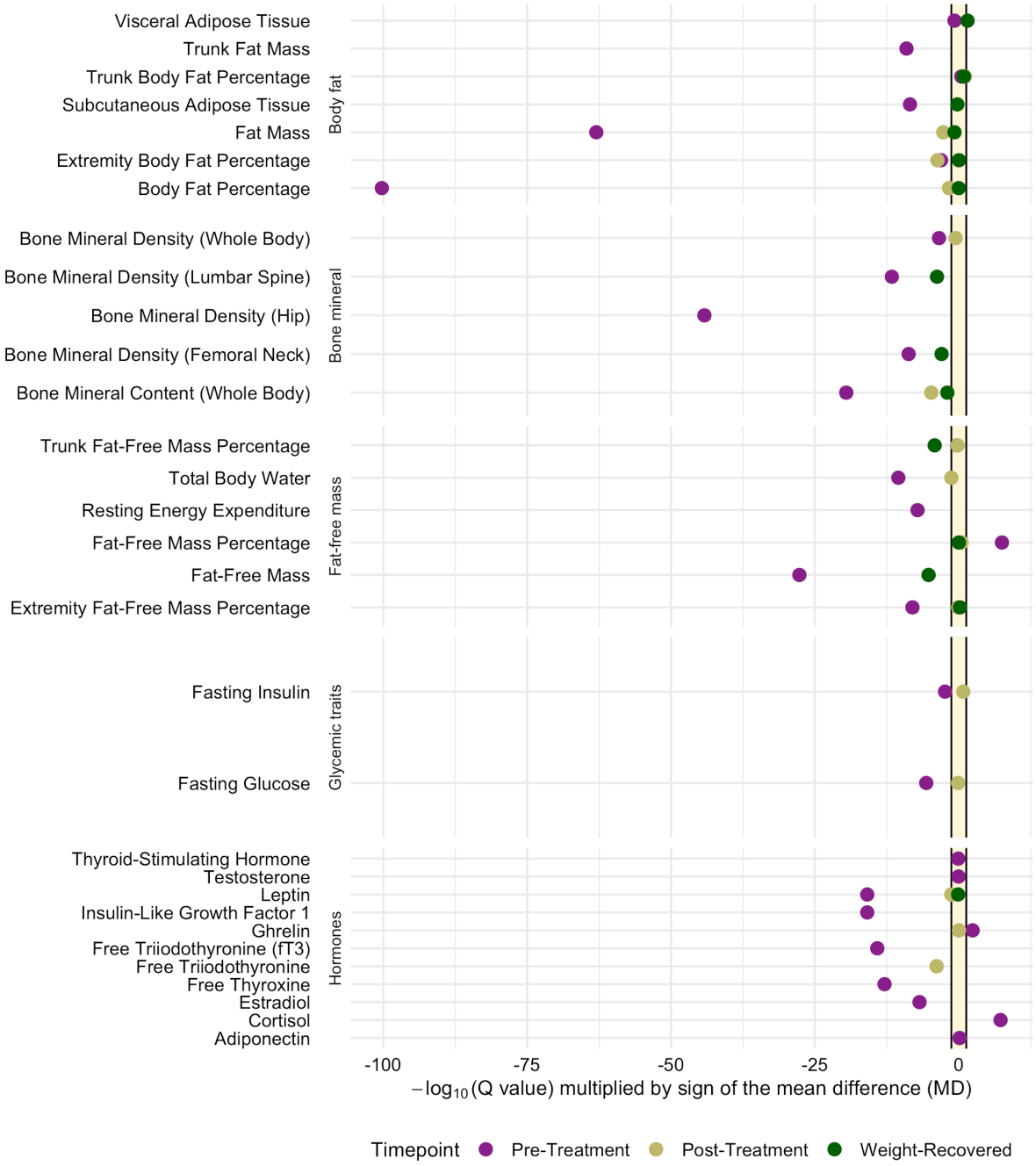

Figure S3 Plot summarising the *Q values* of the meta-analyses comparing anorexia nervosa cases pre-treatment, post-treatment, and after weight recovery with healthy controls. The further the point on the right the larger the mean difference between cases and controls. *Q values* are transformed on the -$\log_{10}$ scale. The horizontal line represents the significance threshold of $Q = 0.05$.

2.5 Cross-sectional meta-analyses of studies comparing acutely-ill/pre-treatment anorexia nervosa patients with healthy controls

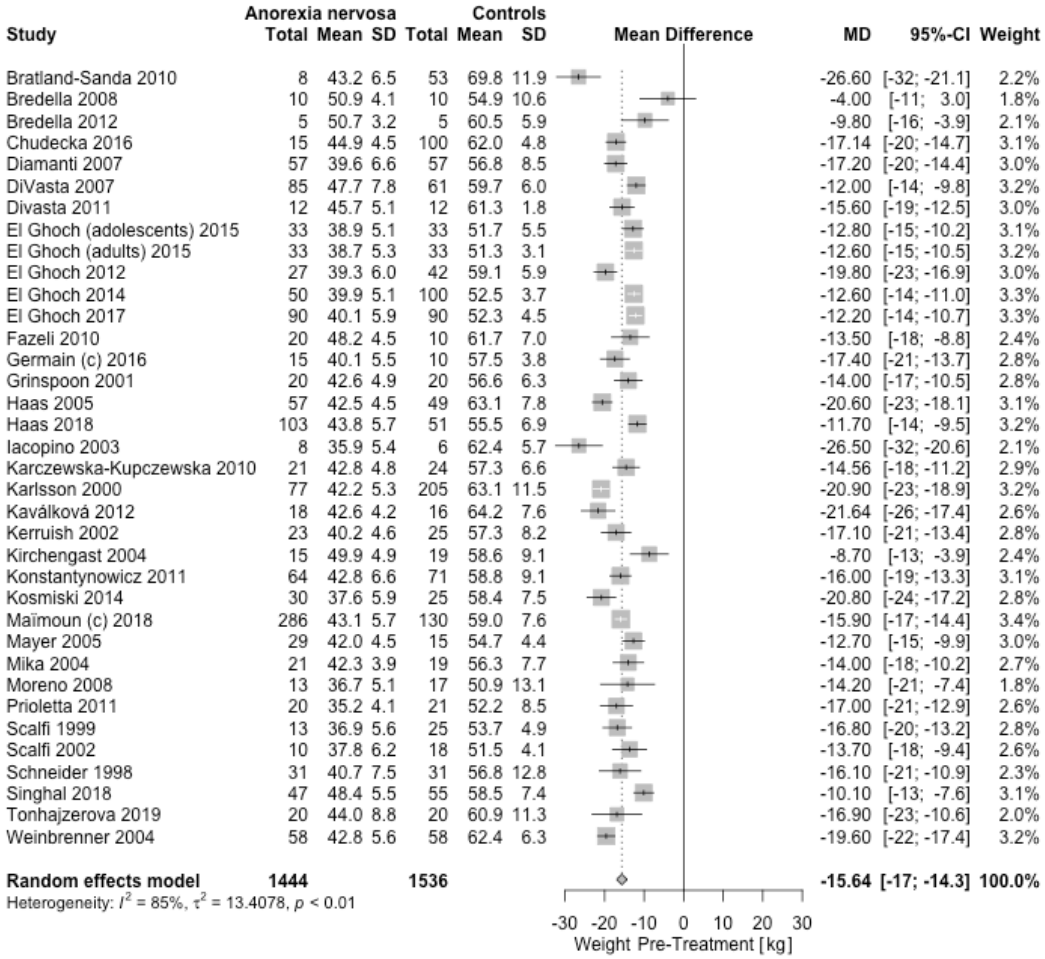

Figure S4. Cross-sectional meta-analysis of studies reporting weight in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Thirty-six samples had the appropriate data for the meta-analysis with 1444 AN cases and 1536 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -15.64 kg; 95% CI: -16.98 , -14.30; $P = 1.27 \times 10^{-115}$) with the mean differences ranging from -26.60 kg to -4.00 kg. Heterogeneity between studies was statistically highly significant ($\tau^2 = 13.41$; $P = 4.12 \times 10^{-30}$; $I^2 = 84.6\%$). C, subtype-combined sample.

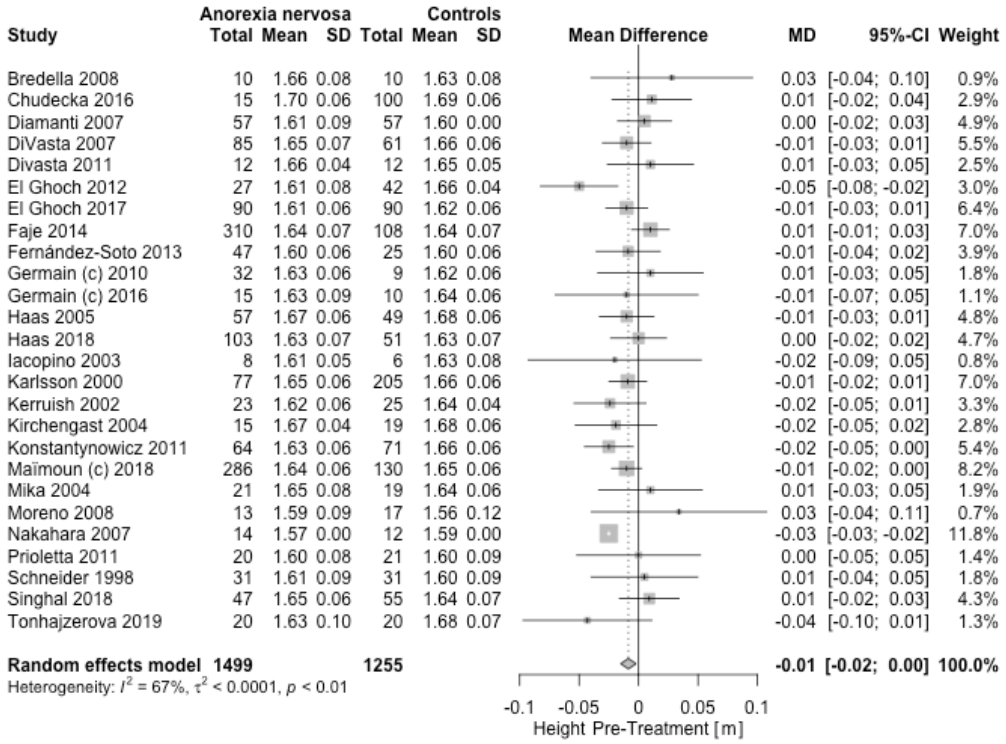

Figure S5. Cross-sectional meta-analysis of studies reporting height in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Twenty-six samples had the appropriate data for the meta-analysis with 1499 AN cases and 1255 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.01 m; 95% CI: -0.02, 0.00; $P = 1.01 \times 10^{-2}$) with the mean differences ranging from -0.05 m to 0.03 m. Heterogeneity between studies was statistically highly significant ($\tau^2 = 0.0001$; $P = 6.86 \times 10^{-7}$; $I^2 = 66.7\%$). C, subtype-combined sample.

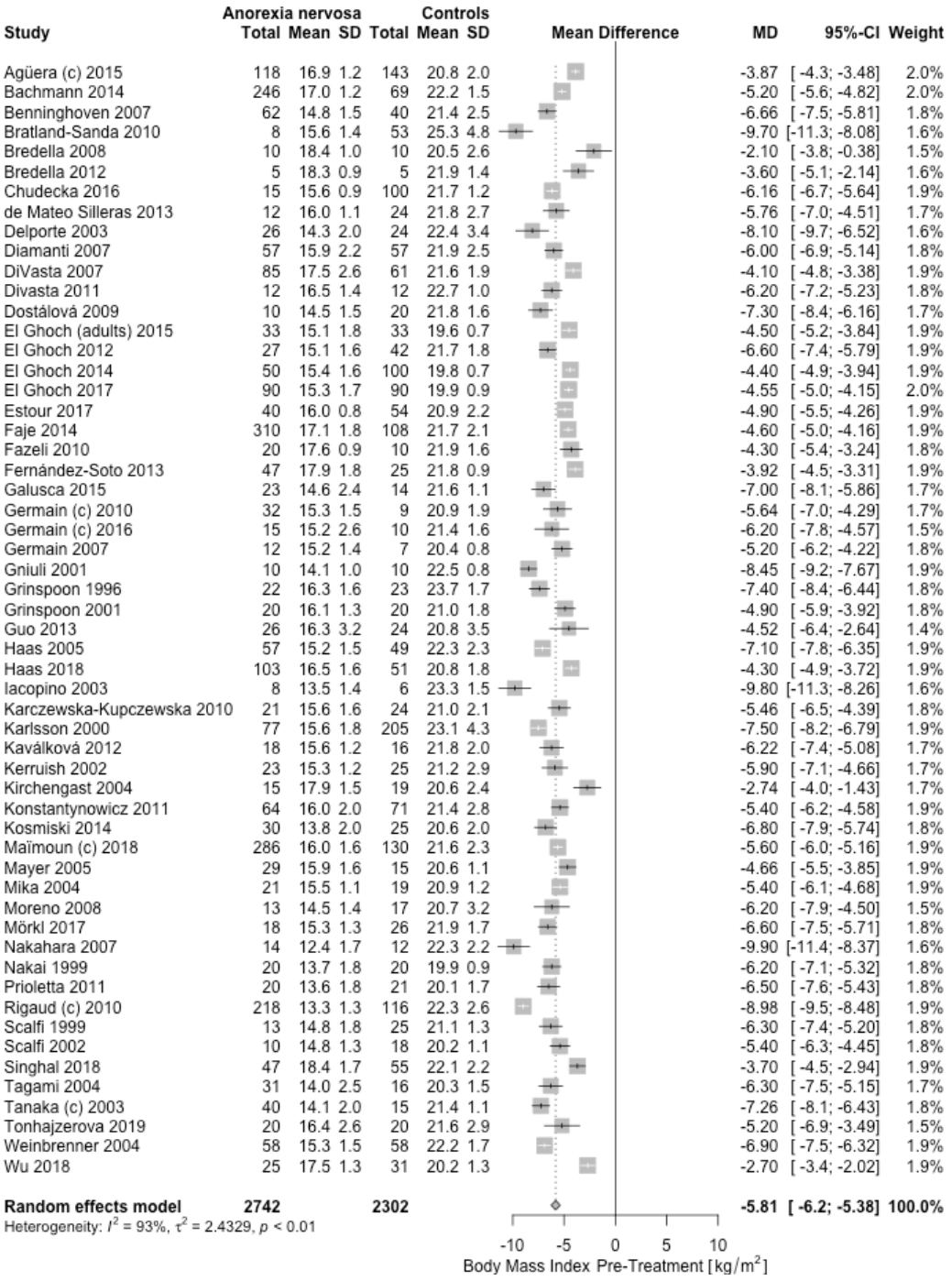

Figure S6. Cross-sectional meta-analysis of studies reporting body mass index in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Fifty-six samples had the appropriate data for the meta-analysis with 2,742 AN cases and 2,302 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -5.81 kg/m^2; 95% CI: -6.25, -5.38; P = 3.22 x 10^{-154}) with the mean differences ranging from -9.90 kg/m^2 to -2.10 kg/m^2. Heterogeneity between studies was statistically significant (τ^2 = 2.43; P = 2.27 x 10^{-140}; I^2 = 93.4%). C, subtype-combined sample.

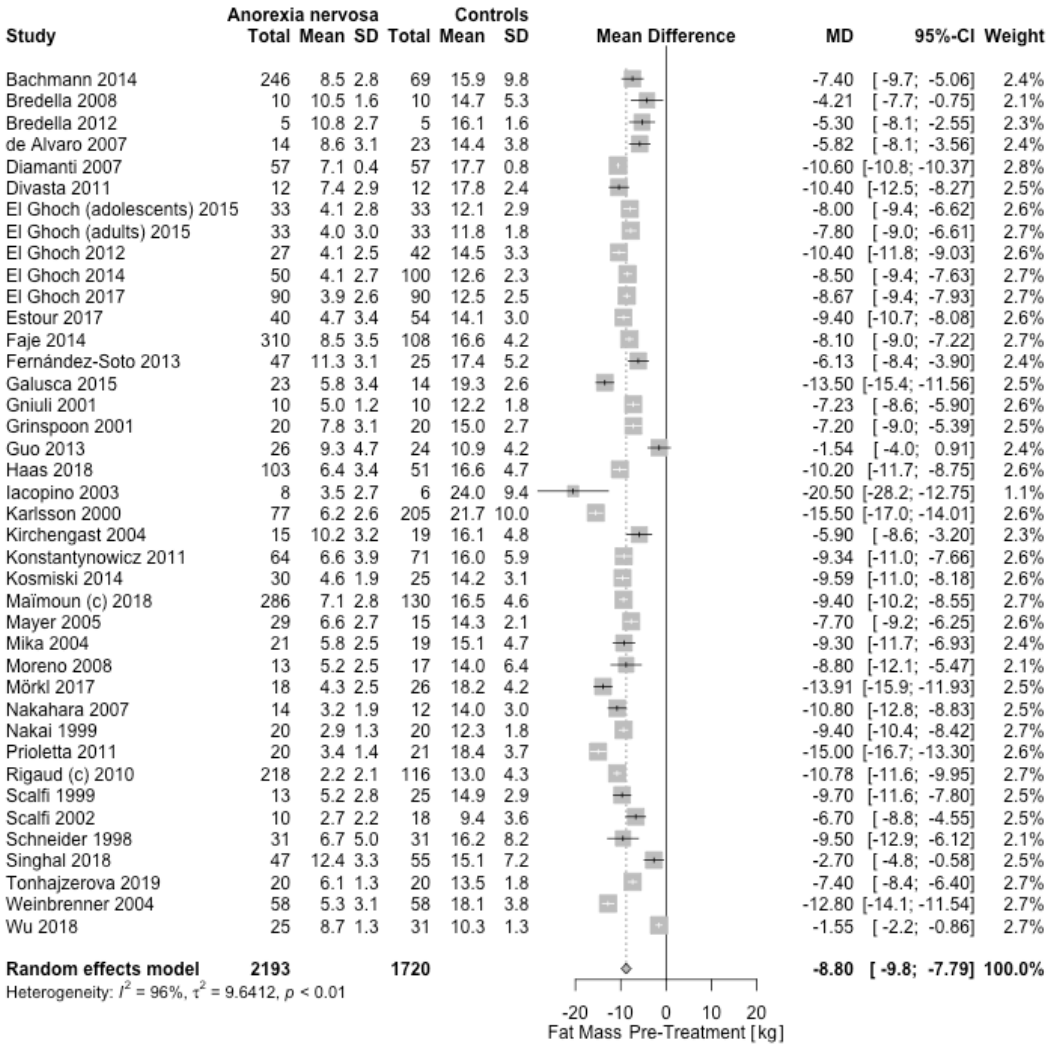

Figure S7. Cross-sectional meta-analysis of studies reporting fat mass in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Forty samples had the appropriate data for the meta-analysis with 2193 AN cases and 1720 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -8.80 kg; 95% CI: -9.81, -7.79; $P = 4.58 \times 10^{-65}$) with the mean differences ranging from -20.50 kg to -1.54 kg. Heterogeneity between studies was statistically significant ($\tau^2 = 9.64$; $P = 2.97 \times 10^{-181}$; $I^2 = 96.0\%$). C, subtype-combined sample.

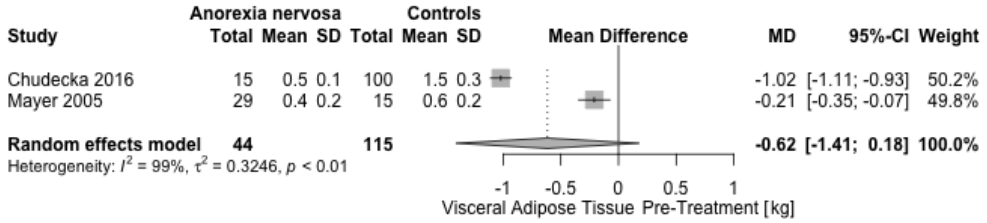

Figure S8. Cross-sectional meta-analysis of studies reporting visceral adipose tissue in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Two samples had the appropriate data for the meta-analysis with 44 AN cases and 115 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.62 kg; 95% CI: -1.41, 0.18; P = 0.13) with the mean differences ranging from -1.02 kg to -0.21 kg. Heterogeneity between studies was statistically significant (τ^2 = 0.32; P = 1.67 x 10^{-22}; I^2 = 99.0%).

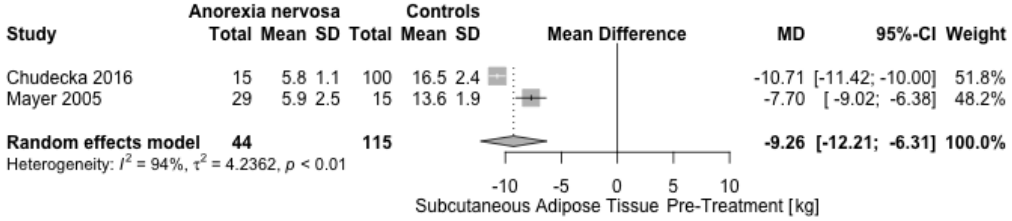

Figure S9. Cross-sectional meta-analysis of studies reporting subcutaneous adipose tissue in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Two samples had the appropriate data for the meta-analysis with 44 AN cases and 115 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -9.26 kg; 95% CI: -12.21, -6.31; P = 7.46 x 10^{-10}) with the mean differences ranging from -10.71 kg to -7.70 kg. Heterogeneity between studies was statistically significant (τ^2 = 4.24; P = 8.63 x 10^{-5}; I^2 = 93.5%).

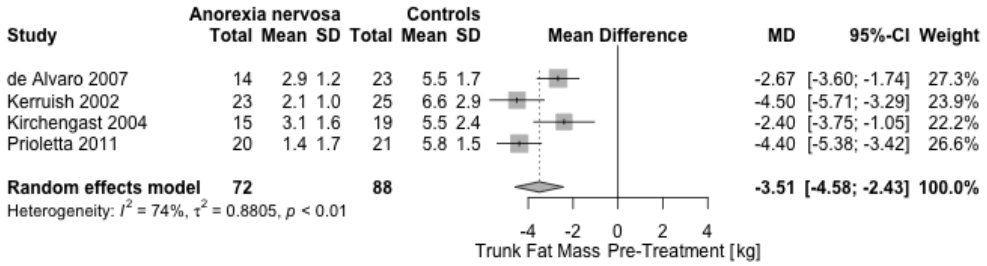

Figure S10. Cross-sectional meta-analysis of studies reporting trunk fat mass in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Four samples had the appropriate data for the meta-analysis with 72 AN cases and 88 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -3.51 kg; 95% CI: -4.58, -2.43; P = 1.65 x 10^{-10}) with the mean differences ranging from -4.50 kg to -2.40 kg. Heterogeneity between studies was statistically significant (τ^2 = 0.88; P = 9.46 x 10^{-3}; I^2 = 73.8%).

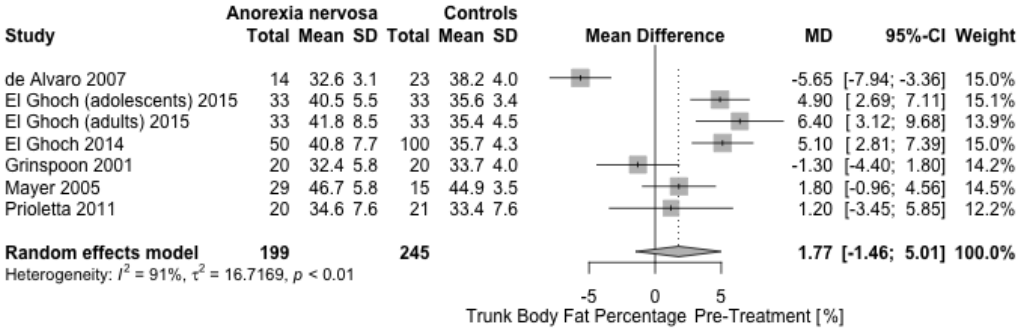

Figure S11. Cross-sectional meta-analysis of studies reporting trunk body fat percentage in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Seven samples had the appropriate data for the meta-analysis with 199 AN cases and 245 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 1.7%; 95% CI: -1.4, 5.0; P = 0.28) with the mean differences ranging from -5.6% to 6.4%. Heterogeneity between studies was statistically significant (τ^2 = 16.72; P = 1.36 x 10^{-12}; I^2 = 91.1%).

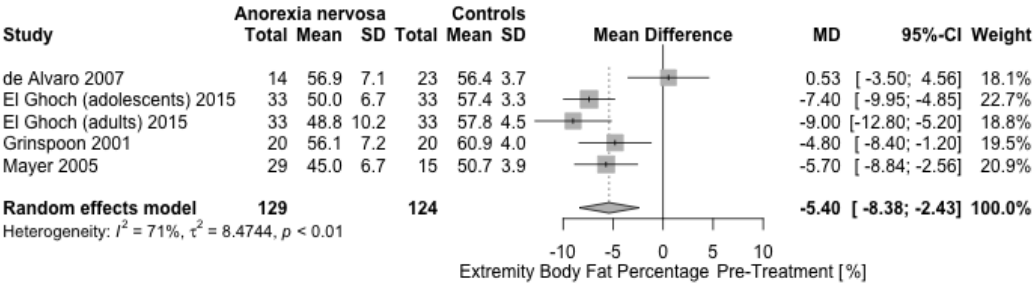

Figure S12. Cross-sectional meta-analysis of studies reporting extremity body fat percentage in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Five samples had the appropriate data for the meta-analysis with 129 AN cases and 124 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -5.4%; 95% CI: -8.3, -2.4; P = 3.74 x 10^{-4}) with the mean differences ranging from -9.0% to 0.5%. Heterogeneity between studies was statistically significant (τ^2 = 8.47; P = 0.01; I^2 = 71.5%).

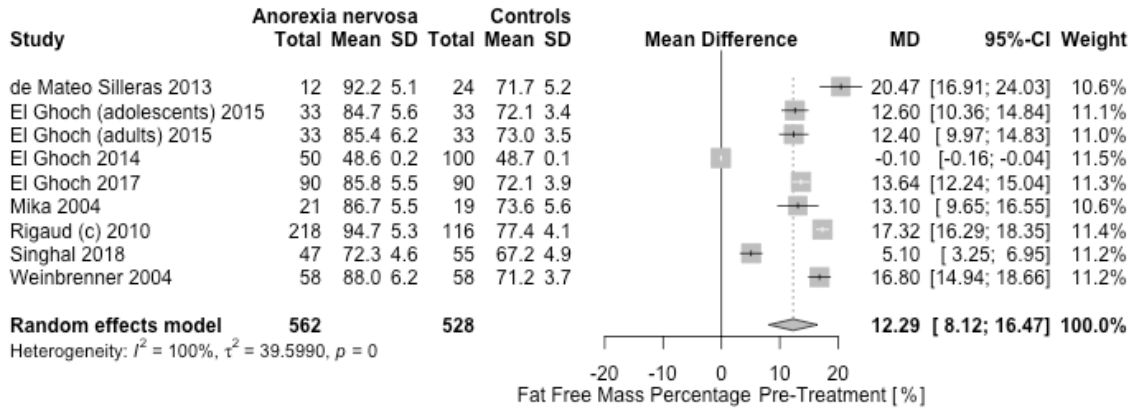

Figure S13. Cross-sectional meta-analysis of studies reporting fat free mass percentage in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Nine samples had the appropriate data for the meta-analysis with 562 AN cases and 528 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 12.3%; 95% CI: 8.1, 16.5; $P = 8.03 \times 10^{-9}$) with the mean differences ranging from -0.1% to 20.5%. Heterogeneity between studies was statistically significant (τ^2 = 39.60; P = 0.00; I^2 = 99.6%). C, subtype-combined sample.

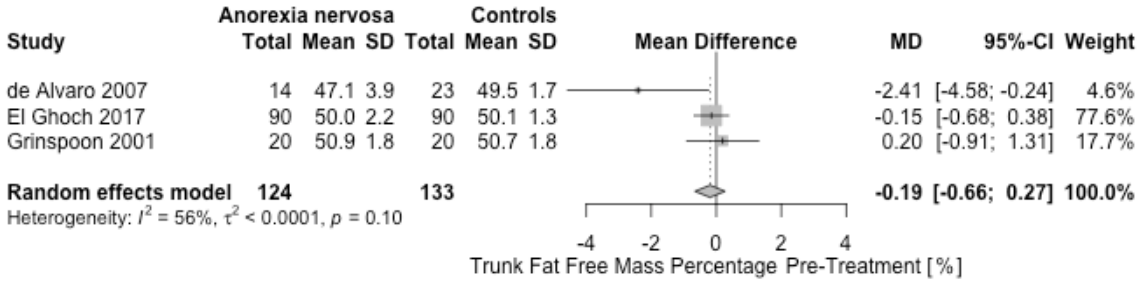

Figure S14. Cross-sectional meta-analysis of studies reporting trunk fat free mass percentage in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Three samples had the appropriate data for the meta-analysis with 124 AN cases and 133 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.2%; 95% CI: -0.6, 0.3; P = 0.42) with the mean differences ranging from -2.4% to 0.2%. Heterogeneity between studies was not statistically significant (τ^2 =0.00; P = 0.10).

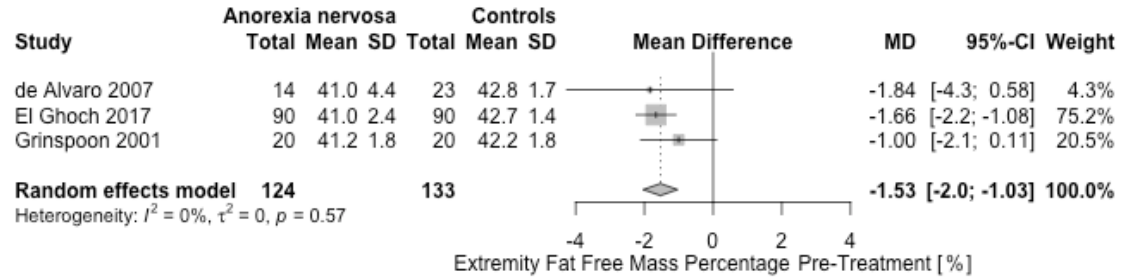

Figure S15. Cross-sectional meta-analysis of studies reporting extremity fat free mass percentage in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Three samples had the appropriate data for the meta-analysis with 124 AN cases and 133 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -1.5%; 95% CI: -2.0, -1.0; $P = 8.07 \times 10^{-9}$) with the mean differences ranging from -1.8% to 1.0%. There was no Heterogeneity between studies (τ^2 =0.00; P = 0.50; I^2 = 0.0%).

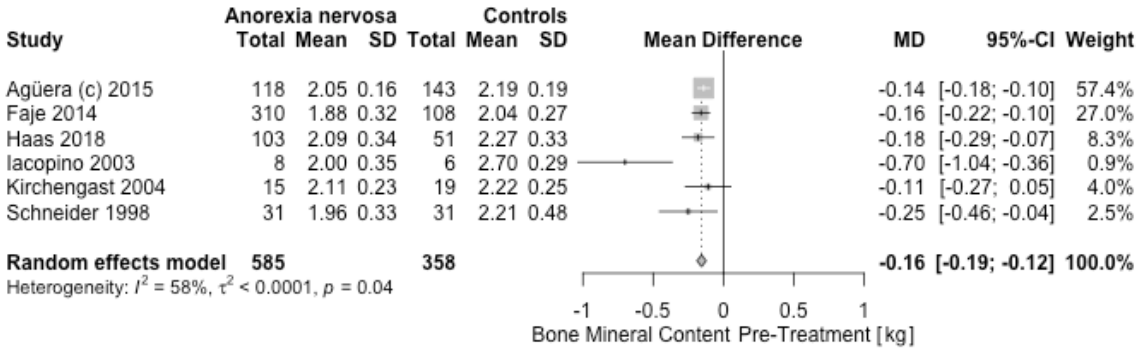

Figure S16. Cross-sectional meta-analysis of studies reporting bone mineral content in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Six samples had the appropriate data for the meta-analysis with 585 AN cases and 358 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.16 kg; 95% CI: -0.19, -0.12; $P = 3.10 \times 10^{-21}$) with the mean differences ranging from -0.70 kg to -0.11 kg. Heterogeneity between studies was statistically significant (τ^2 = 0.00; P = 0.04; I^2 = 58.2%). C, subtype-combined sample.

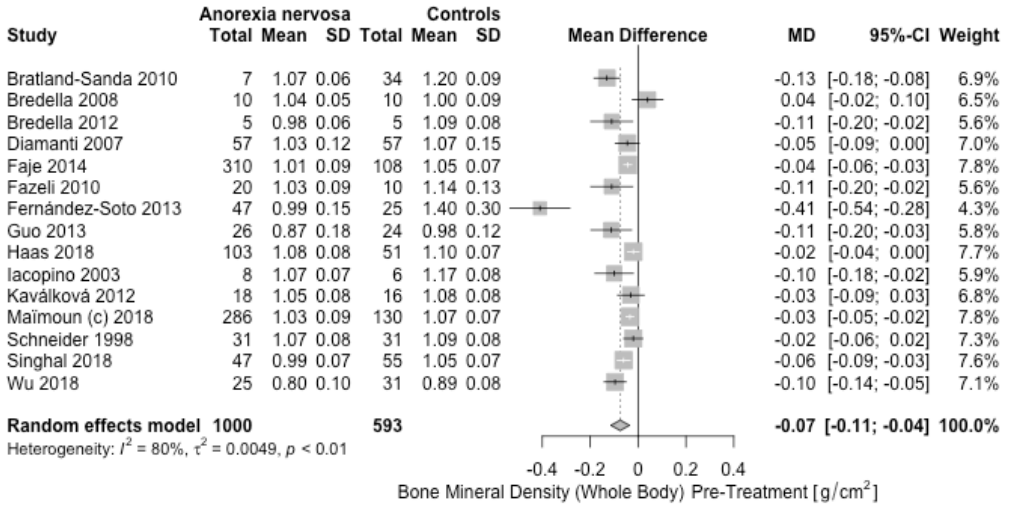

Figure S17. Cross-sectional meta-analysis of studies reporting bone mineral density (whole body) in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Fifteen samples had the appropriate data for the meta-analysis with 1000 AN cases and 593 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.07 g/cm^2; 95% CI: -0,11, -0.04; P = 1.64 x 10^{-4}) with the mean differences ranging from -0.41 g/cm^2 to 0.04 g/cm^2. Heterogeneity between studies was statistically significant (τ^2 = 0.005; P = 1.30 x 10^{-9}; I^2 = 80.3%). C, subtype-combined sample.

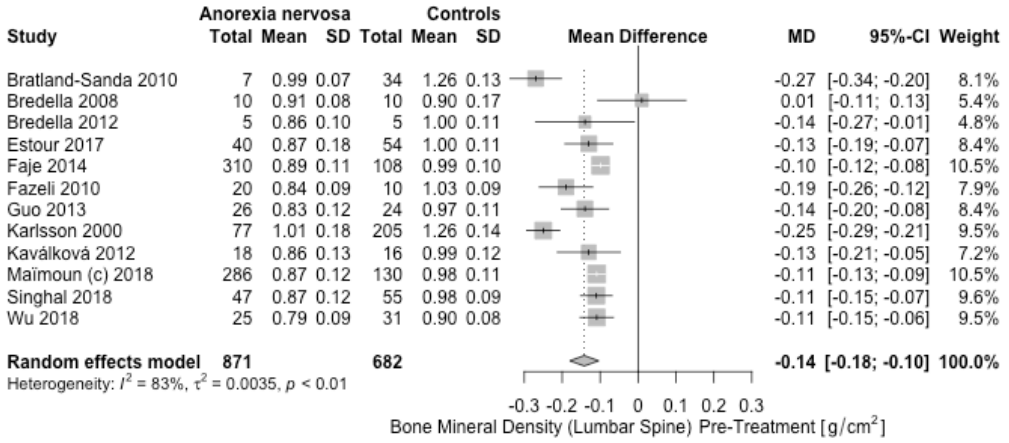

Figure S18. Cross-sectional meta-analysis of studies reporting bone mineral density (lumbar spine) in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Twelve samples had the appropriate data for the meta-analysis with 871 AN cases and 682 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.14 g/cm^2; 95% CI: -0.18, -0.10; P = 4.22 x 10^{-13}) with the mean differences ranging from -0.27 g/cm^2 to 0.01 g/cm^2. Heterogeneity between studies was statistically significant (τ^2 = 0.004; P = 9.28 x 10^{-10}; I^2 = 83.2%). C, subtype-combined sample.

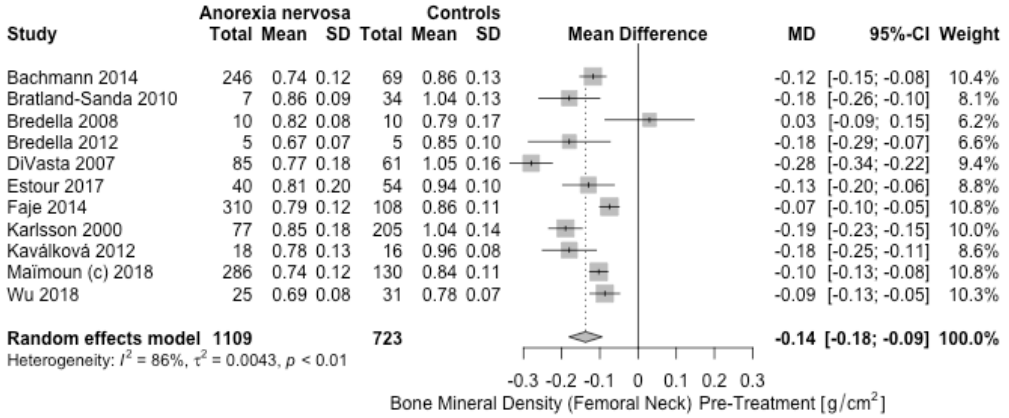

Figure S19. Cross-sectional meta-analysis of studies reporting bone mineral density (femoral neck) in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Eleven samples had the appropriate data for the meta-analysis with 1,109 AN cases and 723 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.14 g/cm^2; 95% CI: -0.18, -0.09; $P = 4.16 \times 10^{-10}$) with the mean differences ranging from -0.28 g/cm^2 to 0.03 g/cm^2. Heterogeneity between studies was statistically significant ($\tau^2 = 0.004$; $P = 2.98 \times 10^{-11}$; $I^2 = 85.9\%$). C, subtype-combined sample.

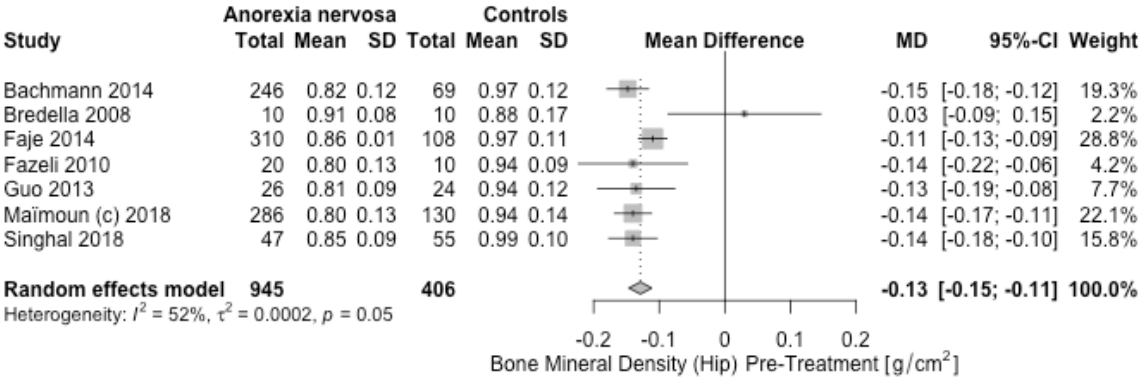

Figure S20. Cross-sectional meta-analysis of studies reporting bone mineral density (hip) in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Seven samples had the appropriate data for the meta-analysis with 945 AN cases and 406 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.13 g/cm^2; 95% CI: -0.15, -0.11; $P = 3.52 \times 10^{-46}$) with the mean differences ranging from -0.15 g/cm^2 to 0.03 g/cm^2. Heterogeneity between studies was statistically significant ($\tau^2 = 2.00 \times 10^{-4}$; $P = 0.05$; $I^2 = 52.0\%$). C, subtype-combined sample.

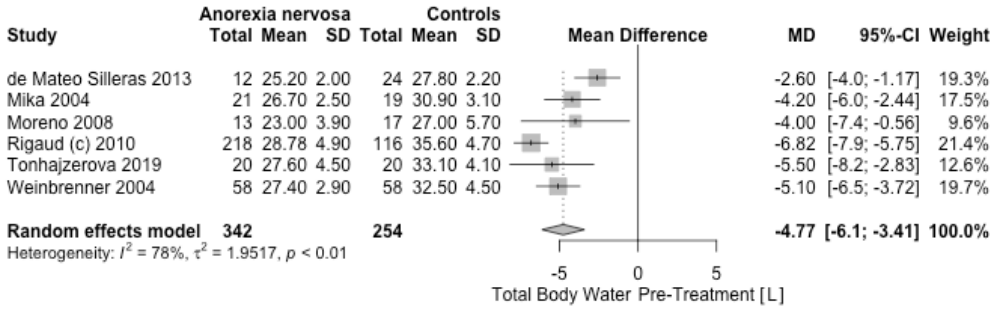

Figure S21. Cross-sectional meta-analysis of studies reporting total body water in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Six samples had the appropriate data for the meta-analysis with 342 AN cases and 254 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -4.77 L; 95% CI: -6.13, -3.41; $P = 5.92 \times 10^{-12}$) with the mean differences ranging from -6.82 L to -2.60 L. Heterogeneity between studies was statistically significant ($\tau^2 = 1.95$; $P = 3.36 \times 10^{-4}$; $I^2 = 78.3\%$). C, subtype-combined sample.

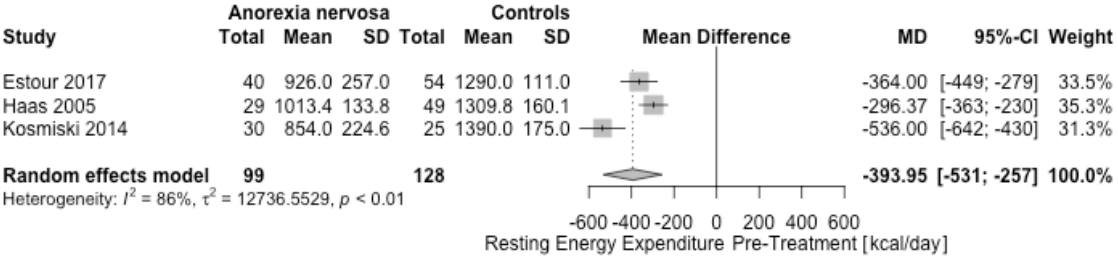

Figure S22. Cross-sectional meta-analysis of studies reporting resting energy expenditure in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Three samples had the appropriate data for the meta-analysis with 99 AN cases and 128 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -393.95 kcal/day; 95% CI: -531.04, -256.86; $P = 1.78 \times 10^{-8}$) with the mean differences ranging from -536.00 kcal/day to -296.37 kcal/day. Heterogeneity between studies was statistically significant ($\tau^2 = 12736.55$; $P = 8.30 \times 10^{-4}$; $I^2 = 85.9\%$).

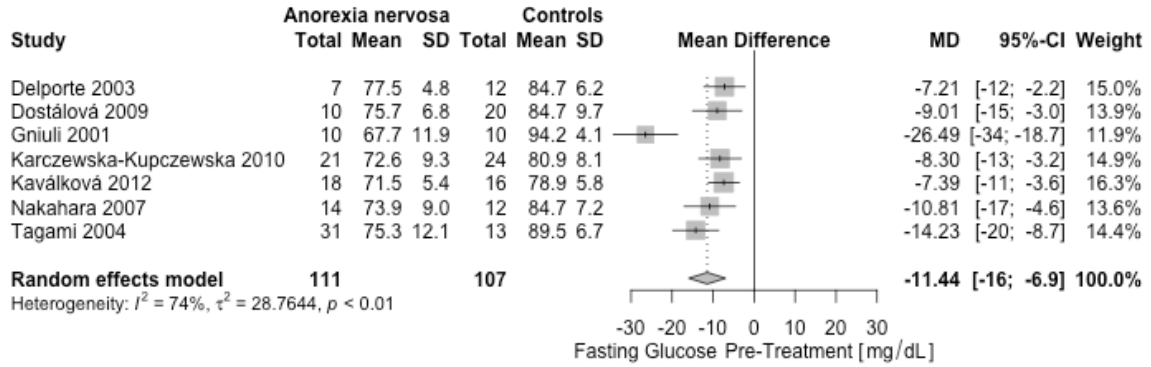

Figure S23. Cross-sectional meta-analysis of studies reporting fasting glucose in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Seven samples had the appropriate data for the meta-analysis with 111 AN cases and 107 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -11.44 mg/dL; 95% CI: -15.95, -6.93; $P = 6.71 \times 10^{-7}$) with the mean differences ranging from -26.49 mg/dL to -7.21 mg/dL. Heterogeneity between studies was statistically highly significant ($\tau^2 = 28.76$; $P = 8.04 \times 10^{-4}$; $I^2 = 73.9\%$).

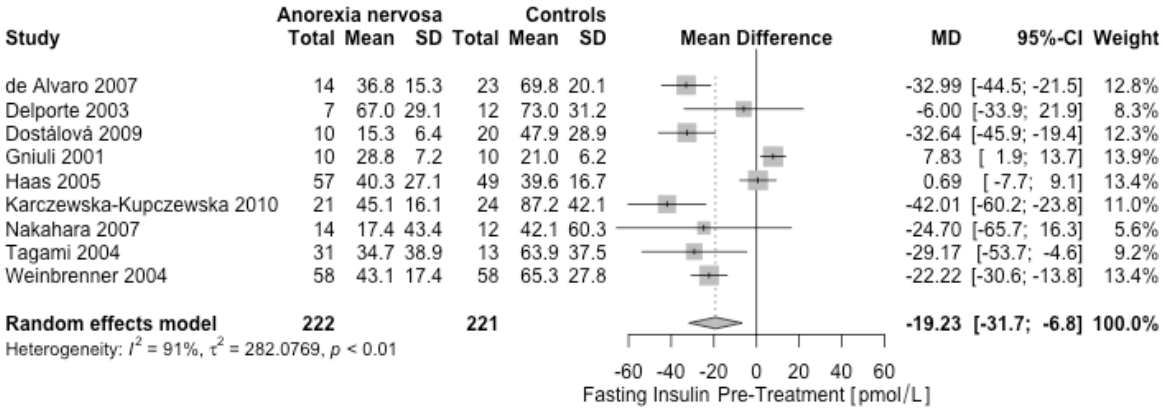

Figure S24. Cross-sectional meta-analysis of studies reporting fasting insulin in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Nine samples had the appropriate data for the meta-analysis with 222 AN cases and 221 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -19.23 pmol/L; 95% CI: -31.68, -6.77; $P = 2.49 \times 10^{-3}$) with the mean differences ranging from -42.01 pmol/L to 7.83 pmol/L. Heterogeneity between studies was statistically highly significant ($\tau^2 = 282.08$; $P = 3.43 \times 10^{-16}$; $I^2 = 91.2\%$).

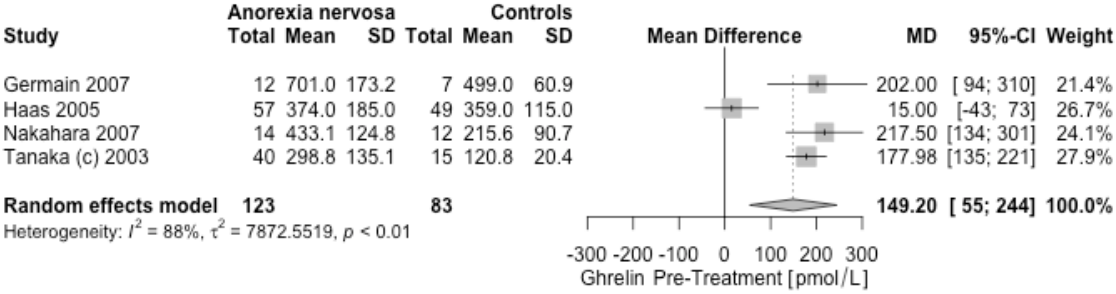

Figure S25. Cross-sectional meta-analysis of studies reporting ghrelin in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Four samples had the appropriate data for the meta-analysis with 123 AN cases and 83 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 149.20 pmol/L; 95% CI: 54.59, 243.81; $P = 2.00 \times 10^{-3}$) with the mean differences ranging from 15.00 pmol/L to 217.50 pmol/L. Heterogeneity between studies was statistically highly significant ($\tau^2 = 7872.55$; $P = 1.19 \times 10^{-5}$; $I^2 = 88.3\%$). C, subtype-combined sample.

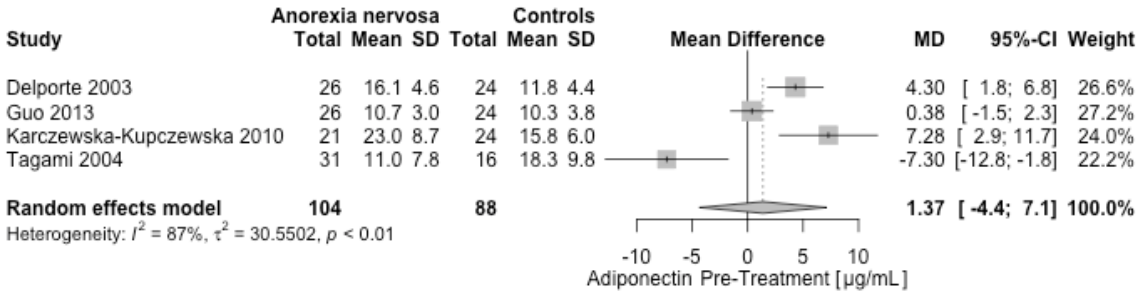

Figure S26. Cross-sectional meta-analysis of studies reporting adiponectin in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Four samples had the appropriate data for the meta-analysis with 104 AN cases and 88 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 1.37 µg/mL; 95% CI: -4.36, 7.11; $P = 0.64$) with the mean differences ranging from -7.30 µg/mL to 7.28 µg/mL. Heterogeneity between studies was statistically significant ($\tau^2 = 30.55$; $P = 5.62 \times 10^{-5}$; $I^2 = 86.6\%$).

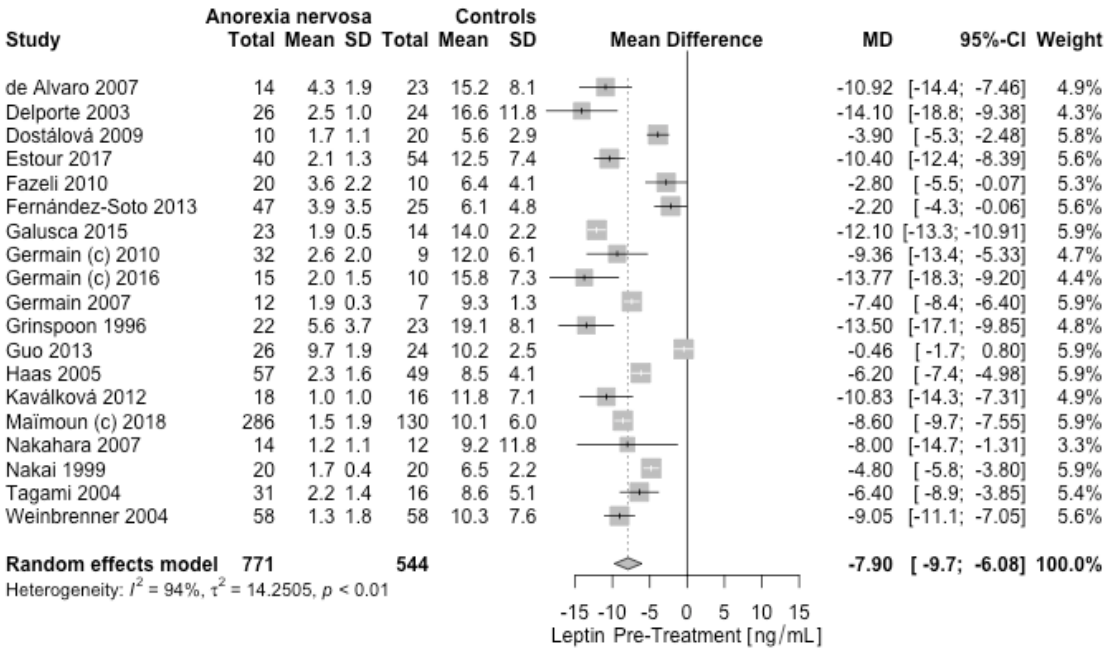

Figure S27. Cross-sectional meta-analysis of studies reporting leptin in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Nineteen samples had the appropriate data for the meta-analysis with 771 AN cases and 544 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -7.90 ng/mL; 95% CI: -9.72, -6.08; $P = 1.55 \times 10^{-17}$) with the mean differences ranging from -14.10 ng/mL to -0.46 ng/mL. Heterogeneity between studies was statistically significant ($\tau^2 = 14.25$; $P = 6.47 \times 10^{-54}$; $I^2 = 94.1\%$). C, subtype-combined sample.

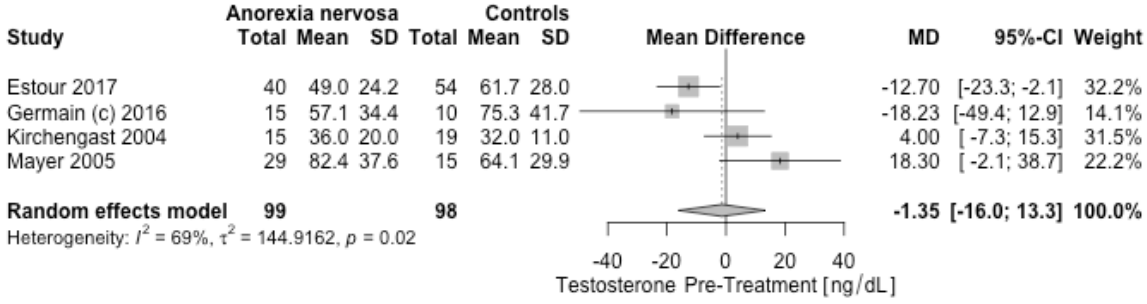

Figure S28. Cross-sectional meta-analysis of studies reporting testosterone in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Four samples had the appropriate data for the meta-analysis with 99 AN cases and 98 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -1.35 ng/dL; 95% CI: -16.03, 13.33; $P = 0.86$) with the mean differences ranging from -18.23 ng/dL to 18.30 ng/dL. Heterogeneity between studies was statistically significant ($\tau^2 = 144.92$; $P = 0.02$; $I^2 = 69.4\%$). C, subtype-combined sample.

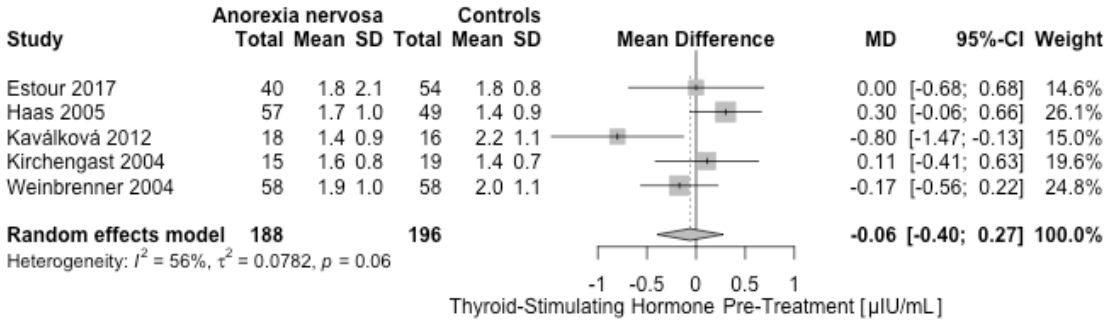

Figure S29. Cross-sectional meta-analysis of studies reporting thyroid-stimulating hormone in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Five samples had the appropriate data for the meta-analysis with 188 AN cases and 196 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.06 µIU/mL; 95% CI: -0.40, 0.27; P = 0.72) with the mean differences ranging from -0.80 µIU/mL to 0.30 µIU/mL. Heterogeneity between studies was not statistically significant (τ^2 = 0.08; P = 0.06; I^2 = 55.5%).

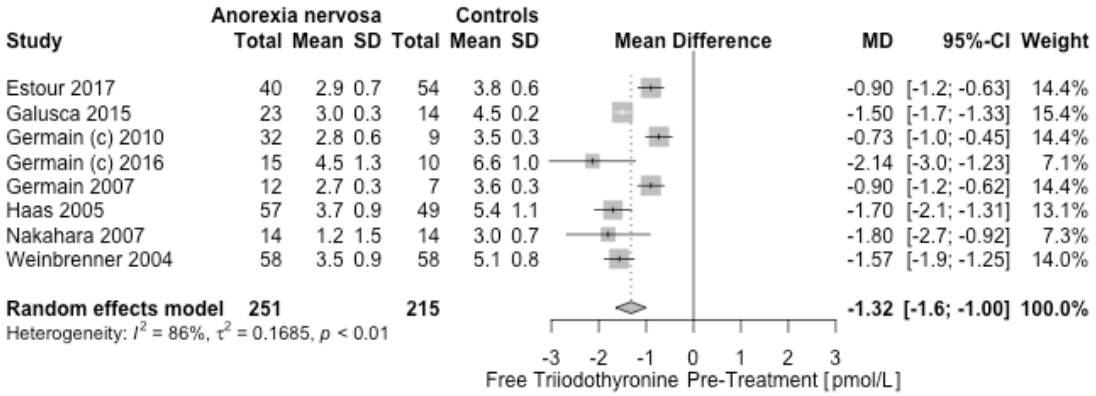

Figure S30. Cross-sectional meta-analysis of studies reporting free triiodothyronine in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Eight samples had the appropriate data for the meta-analysis with 251 AN cases and 215 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -1.32 pmol/L; 95% CI: -1.64, -1.00; $P = 1.09 \times 10^{-15}$) with the mean differences ranging from -2.14 pmol/L to -0.73 pmol/L. Heterogeneity between studies was statistically significant (τ^2 = 0.17; $P = 2.41 \times 10^{-8}$; I^2 = 85.7%). C, subtype-combined sample.

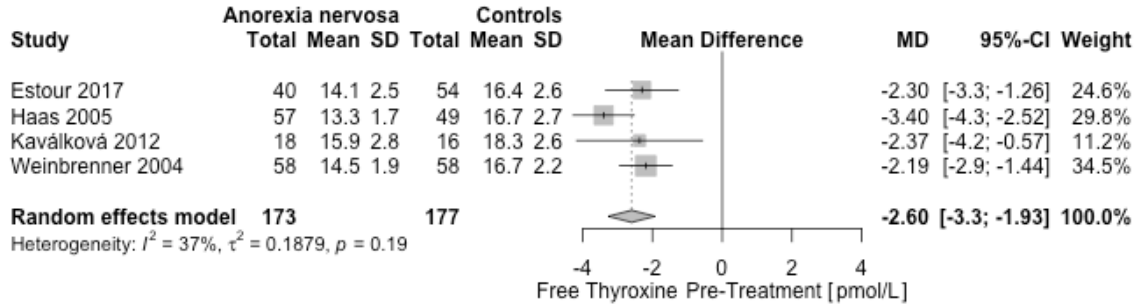

Figure S31. Cross-sectional meta-analysis of studies reporting free thyroxine in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Four samples had the appropriate data for the meta-analysis with 173 AN cases and 177 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -2.60 pmol/L; 95% CI: -3.26, -1.93; $P = 2.09 \times 10^{-14}$) with the mean differences ranging from -3.40 pmol/L to -2.19 pmol/L. Heterogeneity between studies was not statistically significant ($\tau^2 = 0.19$; $P = 0.19$; $I^2 = 36.8\%$).

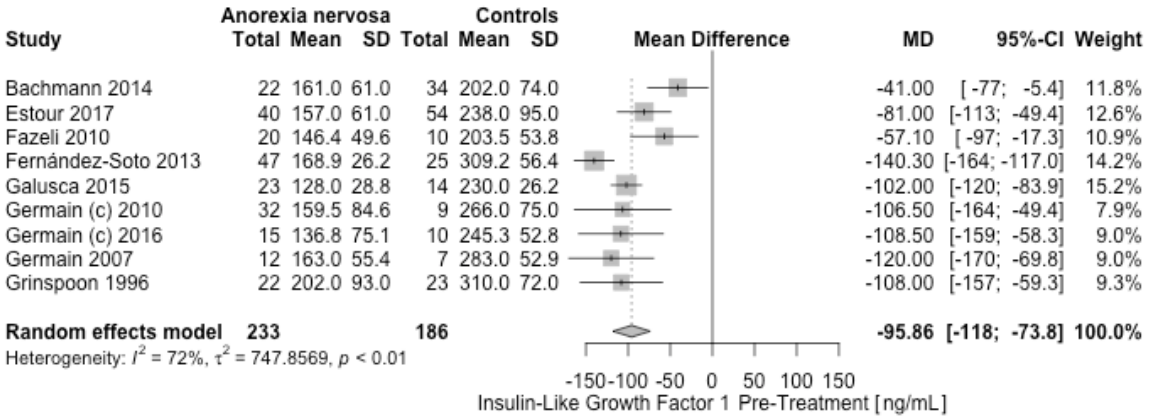

Figure S32. Cross-sectional meta-analysis of studies reporting insulin-like growth factor 1 in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Nine samples had the appropriate data for the meta-analysis with 233 AN cases and 186 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -95.86 ng/mL; 95% CI: -117.93, -73.80; $P = 1.67 \times 10^{-17}$) with the mean differences ranging from -140.30 ng/mL to -41.00 ng/mL. Heterogeneity between studies was statistically significant ($\tau^2 = 747.86$; $P = 3.50 \times 10^{-4}$; $I^2 = 72.2\%$). C, subtype-combined sample.

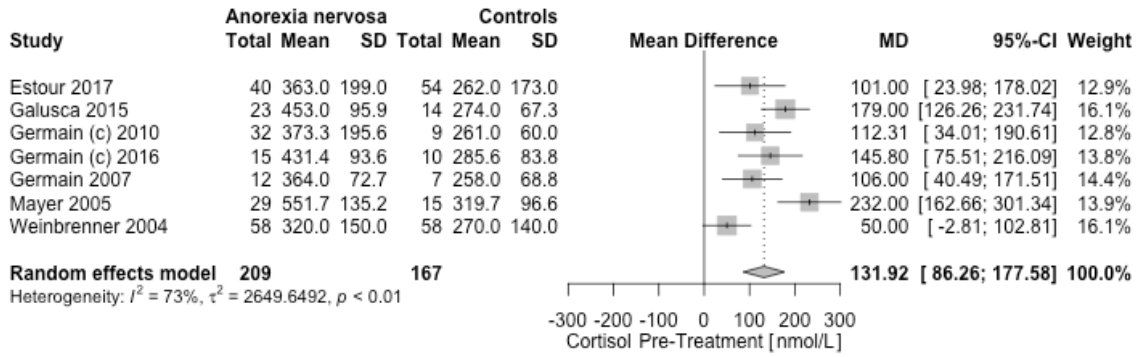

Figure S33. Cross-sectional meta-analysis of studies reporting cortisol in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Seven samples had the appropriate data for the meta-analysis with 209 AN cases and 167 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 131.92 nmol/L; 95% CI: 86.26, 177.58; $P = 1.49 \times 10^{-8}$) with the mean differences ranging from 50.00 nmol/L to 232.00 nmol/L. Heterogeneity between studies was statistically significant ($\tau^2 = 2649.65$; $P = 1.17 \times 10^{-44}$; $I^2 = 72.6\%$). C, subtype-combined sample.

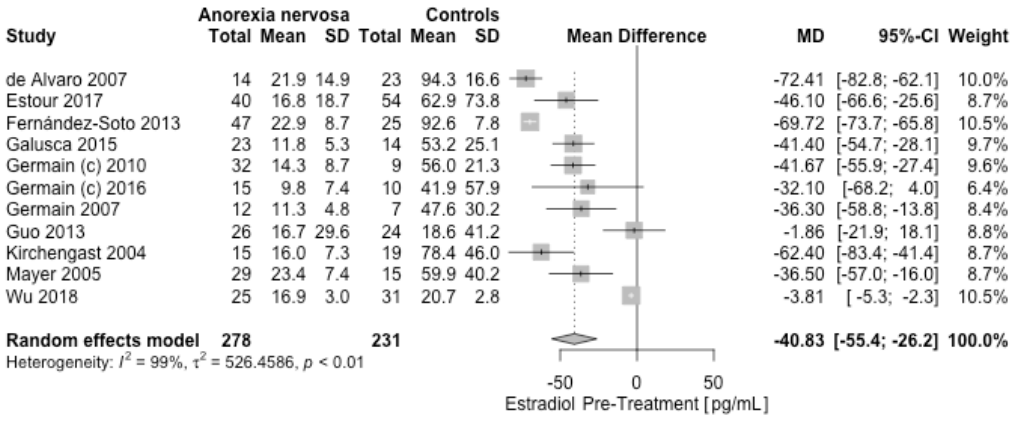

Figure S34. Cross-sectional meta-analysis of studies reporting estradiol in acutely-ill/pre-treatment female anorexia nervosa patients compared with healthy controls. Eleven samples had the appropriate data for the meta-analysis with 278 AN cases and 231 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -40.83 pg/mL; 95% CI: -55.43, -26.23; $P = 4.22 \times 10^{-8}$) with the mean differences ranging from -72.41 pg/mL to -1.86 pg/mL. Heterogeneity between studies was statistically significant ($\tau^2 = 526.46$; $P = 9.60 \times 10^{-237}$; $I^2 = 99.1\%$). C, subtype-combined sample.

2.6 Cross-sectional meta-analyses of studies comparing post-treatment anorexia nervosa patients with healthy controls

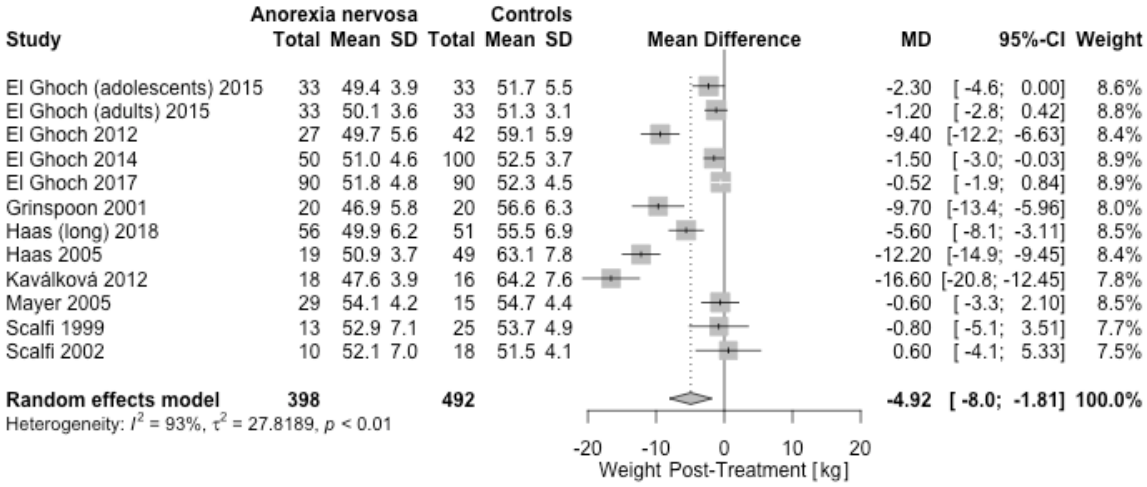

Figure S35. Cross-sectional meta-analysis of studies reporting weight in post-treatment female anorexia nervosa patients compared with healthy controls. Twelve samples had the appropriate data for the meta-analysis with 398 AN cases and 492 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -4.92 kg; 95% CI: -8.03, -1.81; $P = 1.92 \times 10^{-3}$) with the mean differences ranging from -16.60 kg to 0.60 kg. Heterogeneity between studies was statistically highly significant ($\tau^2 = 27.82$; $P = 1.82 \times 10^{-26}$; $I^2 = 92.6\%$). C, subtype-combined sample; long, longitudinal.

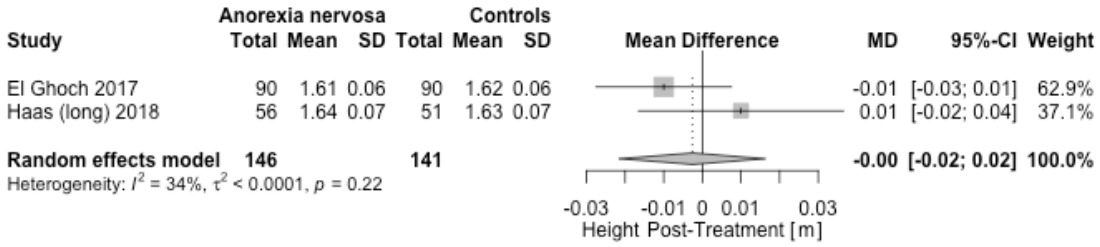

Figure S36. Cross-sectional meta-analysis of studies reporting height in post-treatment female anorexia nervosa patients compared with healthy controls. Two samples had the appropriate data for the meta-analysis with 146 AN cases and 141 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.00 m; 95% CI: -0.02, 0.02; $P = 0.79$) with the mean differences ranging from -0.01 m to 0.01 m. Heterogeneity between studies was not statistically significant ($\tau^2 = 0.00$; $P = 0.22$; $I^2 = 34.1\%$). Long, longitudinal.

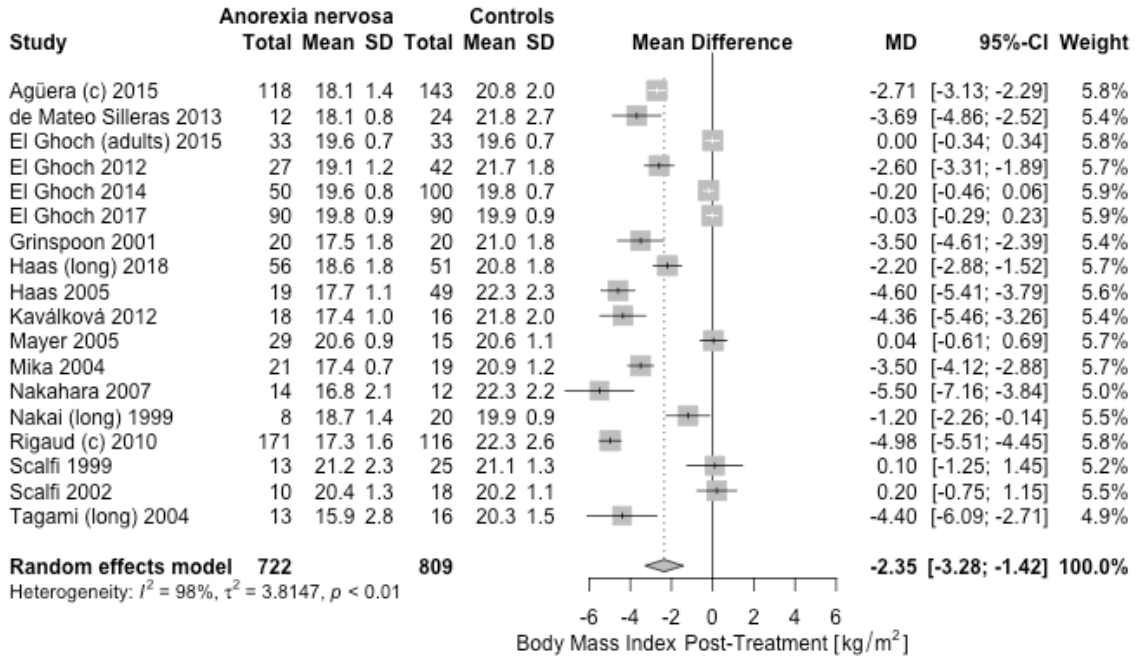

Figure S37. Cross-sectional meta-analysis of studies reporting body mass index in post-treatment female anorexia nervosa patients compared with healthy controls. Eighteen samples had the appropriate data for the meta-analysis with 722 AN cases and 809 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -2.35 kg/m^2; 95% CI: -3.28, -1.42; P = 6.79 x 10^{-7}) with the mean differences ranging from -5.50 kg/m^2 to 0.20 kg/m^2. Heterogeneity between studies was statistically significant (τ^2 = 3.81; P = 3.96 x 10^{-138}; I^2 = 97.6%). C, subtype-combined sample; long, longitudinal.

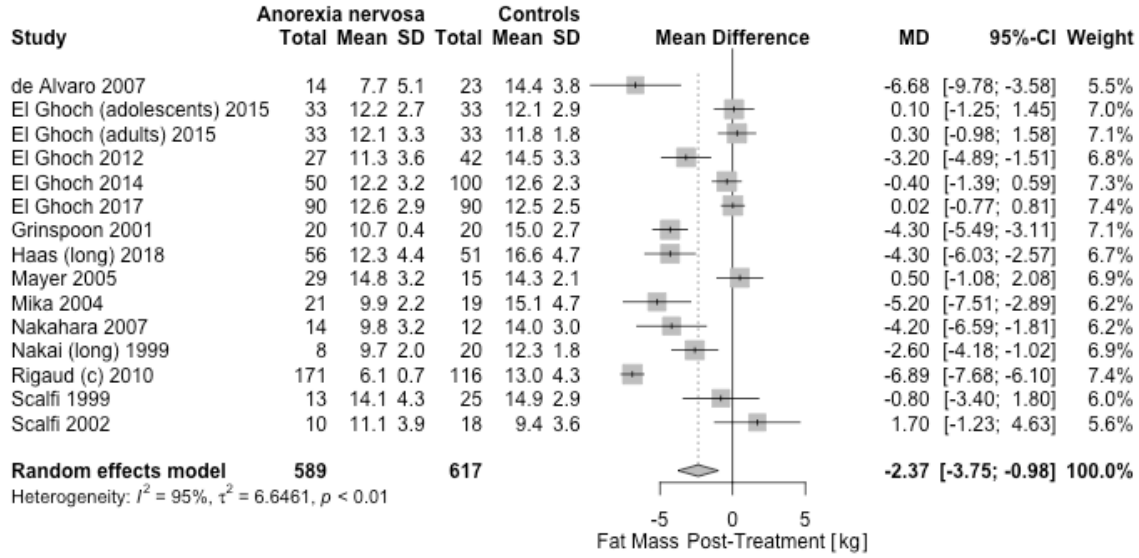

Figure S38. Cross-sectional meta-analysis of studies reporting fat mass in post-treatment female anorexia nervosa patients compared with healthy controls. Fifteen samples had the appropriate data for the meta-analysis with 589 AN cases and 617 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -2.37 kg; 95% CI: -3.75, -0.98; P = 8.29 x 10^{-4}) with the mean differences ranging from -6.89 kg to 1.70 kg. Heterogeneity between studies was statistically highly significant (τ^2 = 6.65; P = 5.45 x 10^{-47}; I^2 = 94.6%). C, subtype-combined sample; long, longitudinal.

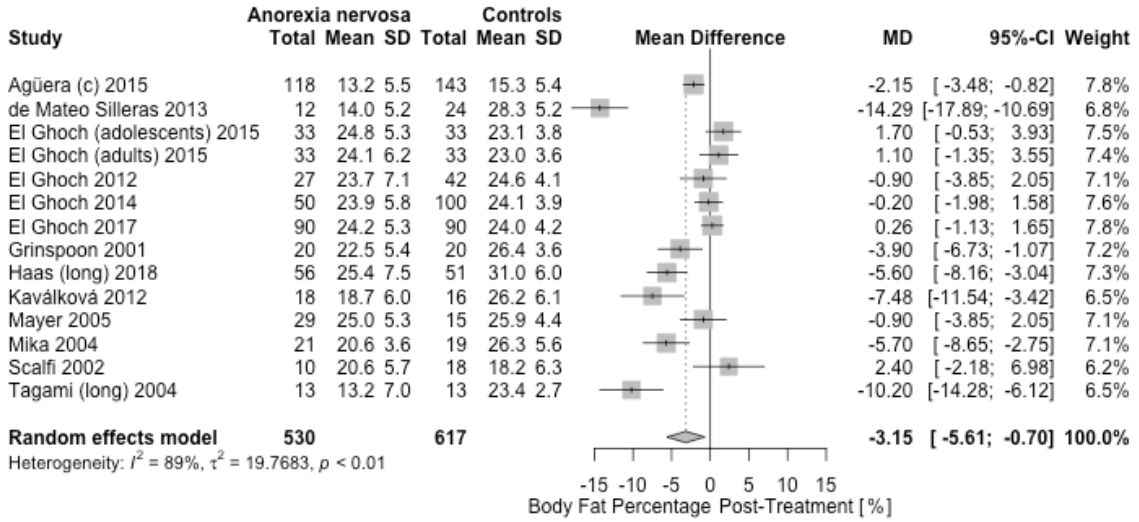

Figure S39. Cross-sectional meta-analysis of studies reporting body fat percentage in post-treatment female anorexia nervosa patients compared with healthy controls. Fourteen samples had the appropriate data for the meta-analysis with 530 AN cases and 617 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -3.15 kg; 95% CI: -5.61, -0.70; P = 0.01) with the mean differences ranging from -14.3% to 2.4%. Heterogeneity between studies was statistically highly significant (τ^2 = 19.77; P = 5.37 x 10^{-19}; I^2 = 89.0%). C, subtype-combined sample; long, longitudinal.

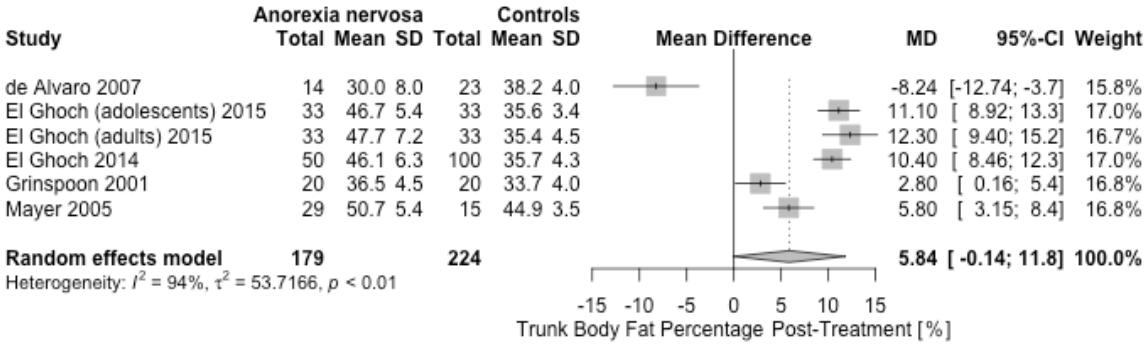

Figure S40. Cross-sectional meta-analysis of studies reporting trunk body fat percentage in post-treatment female anorexia nervosa patients compared with healthy controls. Six samples had the appropriate data for the meta-analysis with 179 AN cases and 224 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 5.8%; 95% CI: -0.1, 11.8; P = 0.06) with the mean differences ranging from -8.2% to 12.3%. Heterogeneity between studies was statistically highly significant (τ^2 = 53.72; P = 7.59 x 10^{-18}; I^2 = 94.4%).

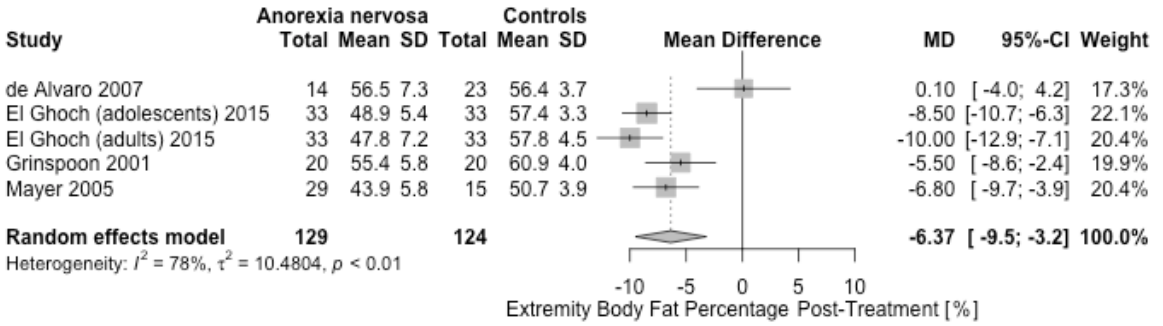

Figure S41. Cross-sectional meta-analysis of studies reporting extremity body fat percentage in post-treatment female anorexia nervosa patients compared with healthy controls. Five samples had the appropriate data for the meta-analysis with 129 AN cases and 124 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -6.4%; 95% CI: -9.52, -3.23; $P = 7.24 \times 10^{-5}$) with the mean differences ranging from -10.0% to 0.0%. Heterogeneity between studies was statistically highly significant ($\tau^2 = 10.48$; $P = 1.09 \times 10^{-3}$; $I^2 = 78.1\%$).

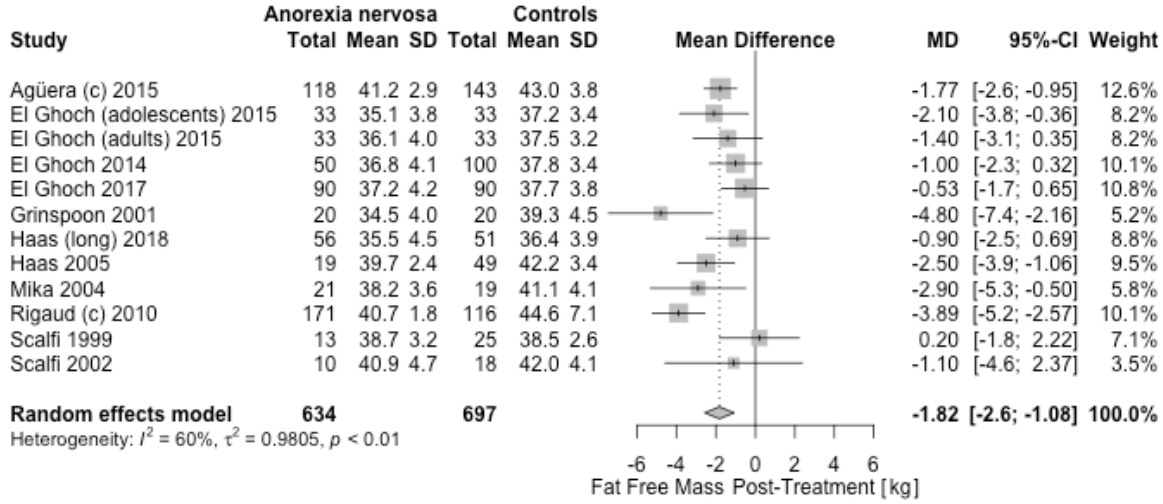

Figure S42. Cross-sectional meta-analysis of studies reporting fat free mass in post-treatment female anorexia nervosa patients compared with healthy controls. Twelve samples had the appropriate data for the meta-analysis with 634 AN cases and 697 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -1.82 kg; 95% CI: -2.57, -1.08; $P = 1.72 \times 10^{-6}$) with the mean differences ranging from -4.80 kg to 0.20 kg. Heterogeneity between studies was statistically highly significant ($\tau^2 = 0.98$; $P = 3.70 \times 10^{-3}$; $I^2 = 60.2\%$). C, subtype-combined sample; long, longitudinal.

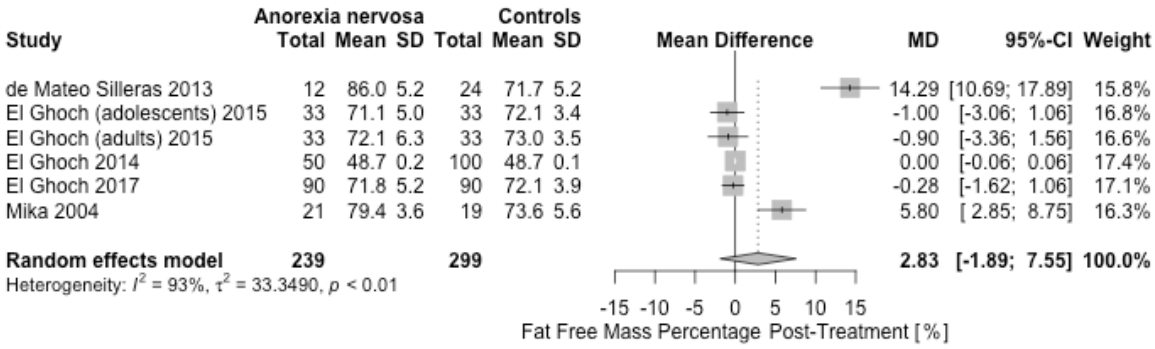

Figure S43. Cross-sectional meta-analysis of studies reporting fat free mass percentage in post-treatment female anorexia nervosa patients compared with healthy controls. Six samples had the appropriate data for the meta-analysis with 239 AN cases and 299 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 2.8%; 95% CI: -1.9, 7.6; P = 0.24) with the mean differences ranging from -1.0% to 14.3%. Heterogeneity between studies was statistically highly significant (τ^2 = 33.35; P = 3.89 x 10^{-15}; I^2 = 93.5%).

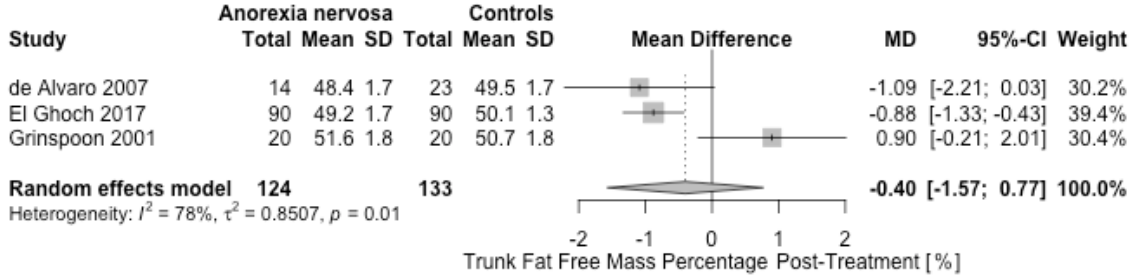

Figure S44. Cross-sectional meta-analysis of studies reporting trunk fat free mass percentage in post-treatment female anorexia nervosa patients compared with healthy controls. Three samples had the appropriate data for the meta-analysis with 124 AN cases and 133 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.4%; 95% CI: -1.6, 0.8; P = 0.50) with the mean differences ranging from -1.1% to 0.9%. Heterogeneity between studies was statistically significant (τ^2 = 0.85; P = 0.01; I^2 = 77.9%).

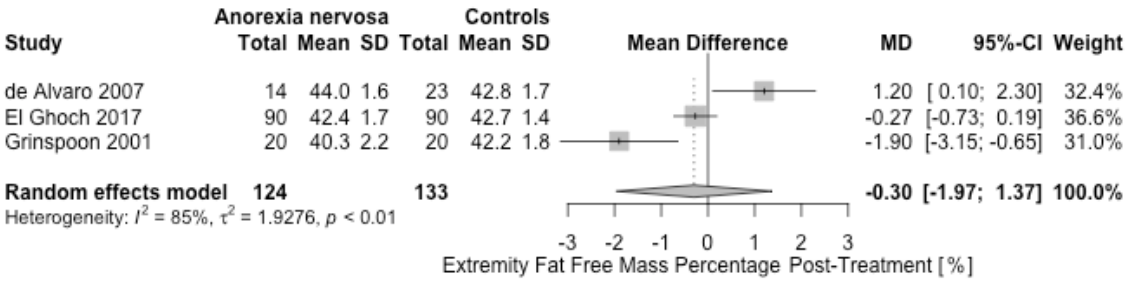

Figure S45. Cross-sectional meta-analysis of studies reporting extremity fat free mass percentage in post-treatment female anorexia nervosa patients compared with healthy controls. Three samples had the appropriate data for the meta-analysis with 124 AN cases and 133 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.3%; 95% CI: -1.97, 1.37; P = 0.73) with the mean differences ranging from -1.9% to 1.2%. Heterogeneity between studies was statistically significant (τ^2 = 1.93; P = 1.26 x 10^{-3}; I^2 = 85.0%).

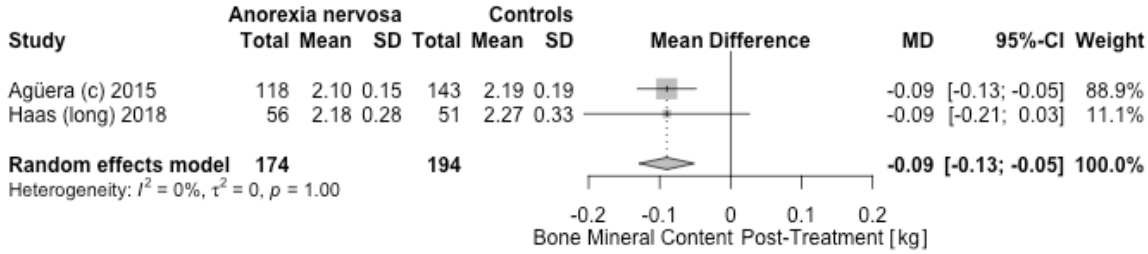

Figure S46. Cross-sectional meta-analysis of studies reporting bone mineral content in post-treatment female anorexia nervosa patients compared with healthy controls. Two samples had the appropriate data for the meta-analysis with 174 AN cases and 194 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.09 kg; 95% CI: -0.13, -0.05; $P = 5.75 \times 10^{-6}$) with the mean differences ranging from -0.09 kg to -0.09 kg. There was no Heterogeneity between studies ($\tau^2 = 0.00$; $P = 1.00$; $I^2 = 0.0\%$). C, subtype-combined sample; long, longitudinal.

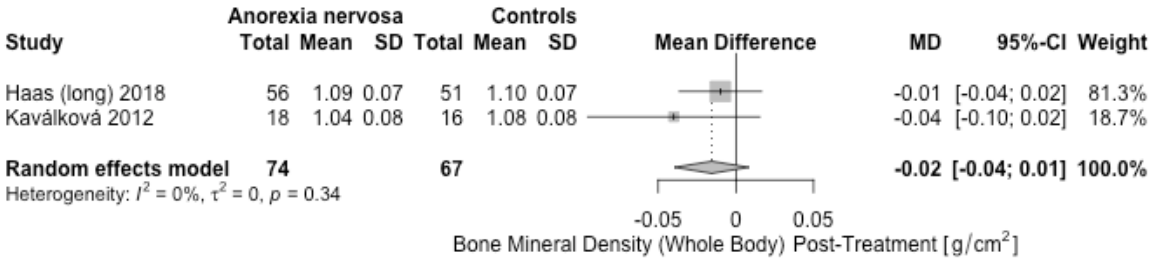

Figure S47. Cross-sectional meta-analysis of studies reporting bone mineral density (whole body) content in post-treatment female anorexia nervosa patients compared with healthy controls. Two samples had the appropriate data for the meta-analysis with 74 AN cases and 67 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.02 g/cm^2; 95% CI: -0.04, 0.01; $P = 0.20$) with the mean differences ranging from -0.04 g/cm^2 to -0.01 g/cm^2. There was no Heterogeneity between studies ($\tau^2 = 0.00$; $P = 0.34$; $I^2 = 0.0\%$). long, longitudinal.

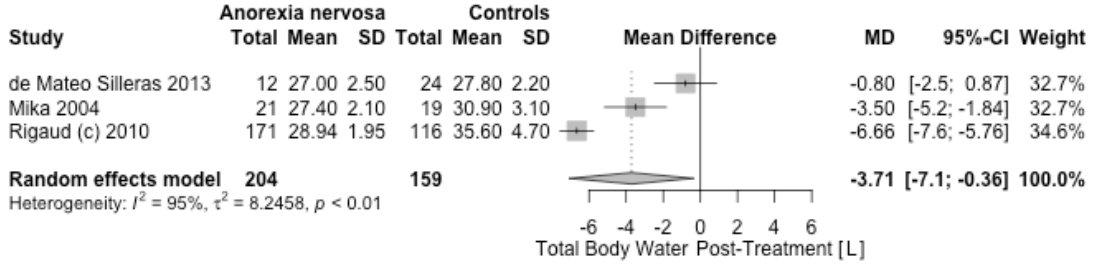

Figure S48. Cross-sectional meta-analysis of studies reporting total body water in post-treatment female anorexia nervosa patients compared with healthy controls. Three samples had the appropriate data for the meta-analysis with 204 AN cases and 159 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -3.71 L; 95% CI: -7.07, -0.36; $P = 0.03$) with the mean differences ranging from -6.66 L to -0.80 L. Heterogeneity between studies was statistically highly significant ($\tau^2 = 8.25$; $P = 1.59 \times 10^{-9}$; $I^2 = 95.1\%$). C, subtype-combined sample.

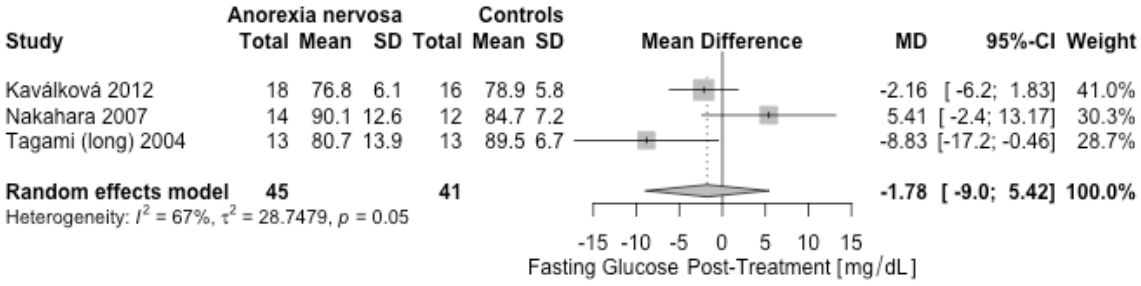

Figure S49. Cross-sectional meta-analysis of studies reporting fasting glucose in post-treatment female anorexia nervosa patients compared with healthy controls. Three samples had the appropriate data for the meta-analysis with 45 AN cases and 41 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -1.78 mg/dL; 95% CI: -8.98, 5.42; P = 0.63) with the mean differences ranging from -8.83 mg/dL to 5.41 mg/dL. Heterogeneity between studies was statistically significant (τ^2 = 28.75; P = 0.05; I^2 = 66.9%).

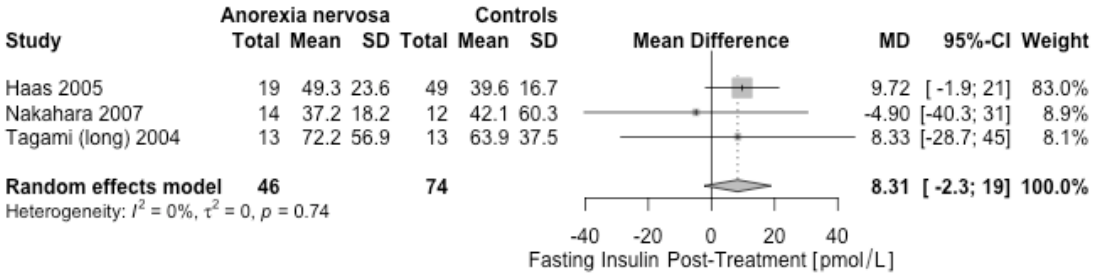

Figure S50. Cross-sectional meta-analysis of studies reporting fasting insulin in post-treatment female anorexia nervosa patients compared with healthy controls. Three samples had the appropriate data for the meta-analysis with 46 AN cases and 74 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 8.31 pmol/L; 95% CI: -2.26, 18.87; P = 0.12) with the mean differences ranging from -4.90 pmol/L to 9.72 pmol/L. There was no Heterogeneity between studies (τ^2 = 0.00; P = 0.74; I^2 = 0.0%). Long, longitudinal.

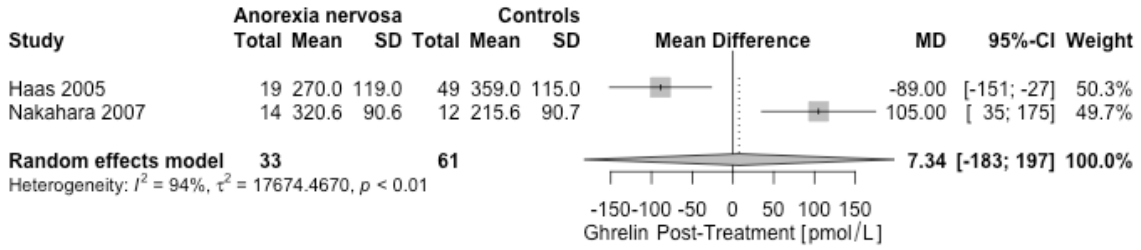

Figure S51. Cross-sectional meta-analysis of studies reporting ghrelin in post-treatment female anorexia nervosa patients compared with healthy controls. Two samples had the appropriate data for the meta-analysis with 33 AN cases and 61 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 7.34 pmol/L; 95% CI: -182.77, 197.45; P = 0.94) with the mean differences ranging from -89.00 pmol/L to 105.00 pmol/L. Heterogeneity between studies was statistically significant (τ^2 = 17674.47; P = 4.98 x 10^{-5} ; I^2 = 93.9%).

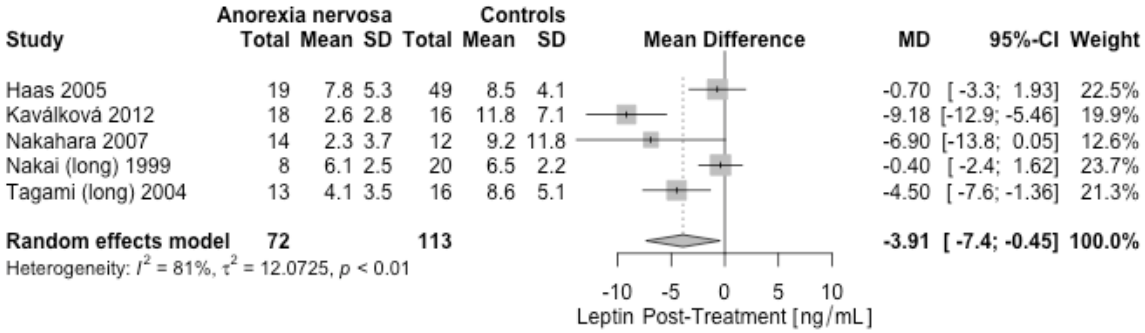

Figure S52. Cross-sectional meta-analysis of studies reporting leptin in post-treatment female anorexia nervosa patients compared with healthy controls. Five samples had the appropriate data for the meta-analysis with 72 AN cases and 113 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -3.91 ng/mL; 95% CI: -7.37, -0.45; P = 0.03) with the mean differences ranging from -9.18 ng/mL to -0.40 ng/mL. Heterogeneity between studies was statistically significant (τ^2 =12.07; P = 2.59 x 10^{-4} ; I^2 = 81.3%). Long, longitudinal.

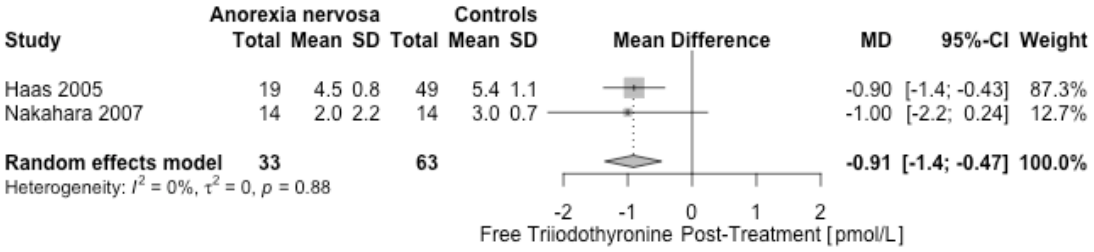

Figure S53. Cross-sectional meta-analysis of studies reporting free triiodothyronine in post-treatment female anorexia nervosa patients compared with healthy controls. Two samples had the appropriate data for the meta-analysis with 33 AN cases and 63 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.91 pmol/L; 95% CI: -1.36, -0.47; P = 5.26 x 10^{-5}) with the mean differences ranging from -1.00 pmol/L to -0.90 pmol/L. There was no Heterogeneity between studies (τ^2 = 0.00; P = 0.88; I^2 = 0.0%).

2.7 Longitudinal meta-analyses of studies comparing anorexia nervosa patients pre- and post-treatment

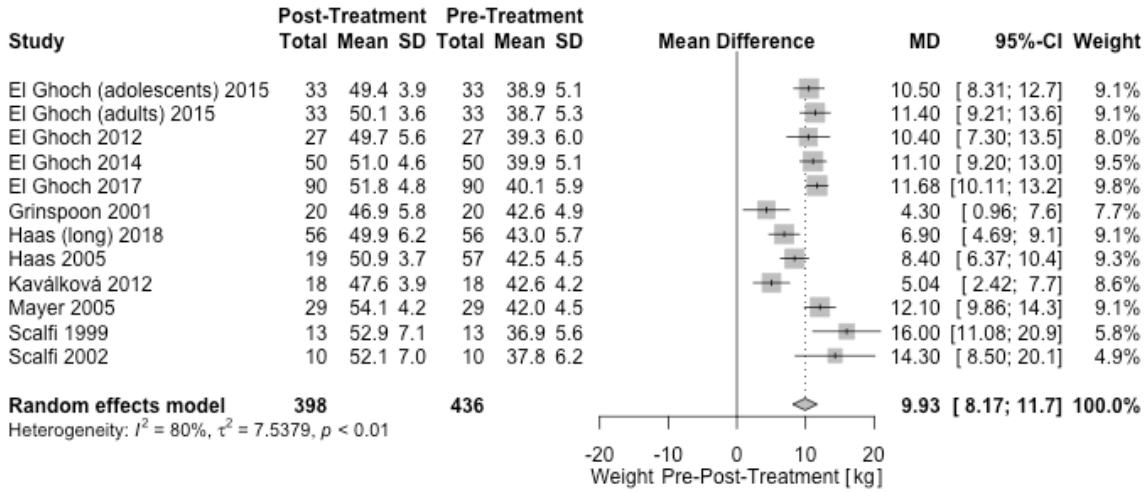

Figure S54. Longitudinal meta-analysis of studies reporting weight in female anorexia nervosa patients pre- and post-treatment. Twelve samples had the appropriate data for the meta-analysis with 398 AN cases and 436 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 9.93 kg; 95% CI: 8.17, 11.68; P = 1.44 x 10^{-28}) with the mean differences ranging from 4.30 kg to 16.00 kg. Heterogeneity between studies was statistically highly significant (τ^2 = 7.54; P = 1.35 x 10^{-7}; I^2 = 80.0%). C, subtype-combined sample.

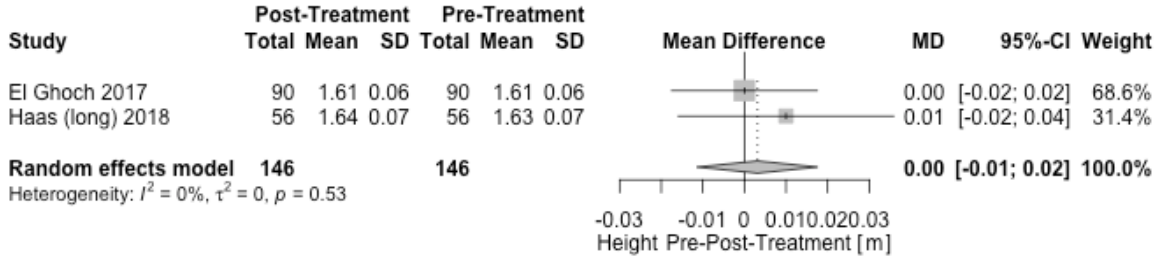

Figure S55. Longitudinal meta-analysis of studies reporting height in female anorexia nervosa patients pre- and post-treatment. Two samples had the appropriate data for the meta-analysis with 146 AN cases and 146 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 0.00 m; 95% CI: -0.01, 0.02; P = 0.67) with the mean differences ranging from 0.00 m to 0.01 m. There was no Heterogeneity between studies (τ^2 = 0.00; P = 0.53; I^2 = 0.0%). C, subtype-combined sample.

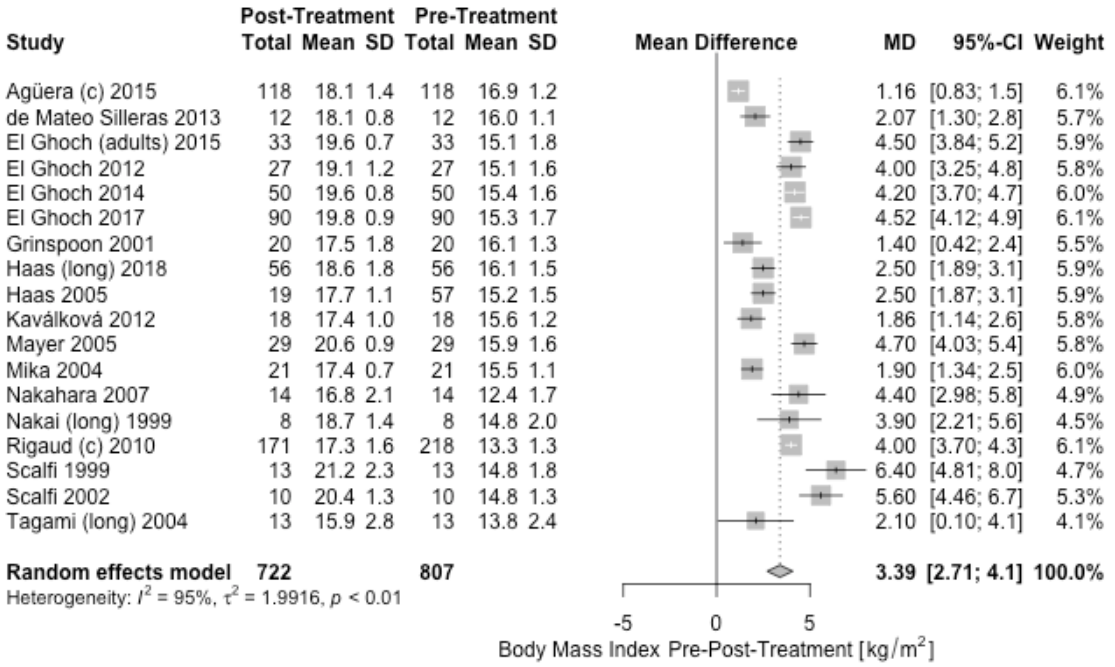

Figure S56. Longitudinal meta-analysis of studies reporting body mass index in female anorexia nervosa patients pre- and post-treatment. Eighteen samples had the appropriate data for the meta-analysis with 722 AN cases and 807 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 3.39 kg/m^2 kg; 95% CI: 2.71, 4.08; P = 4.19 x 10^{-22}) with the mean differences ranging from 1.16 kg/m^2 to 6.40 kg/m^2. Heterogeneity between studies was statistically highly significant (τ^2 = 1.99; P = 8.54 x 10^{-68}; I^2 = 95.0%). C, subtype-combined sample; long, longitudinal.

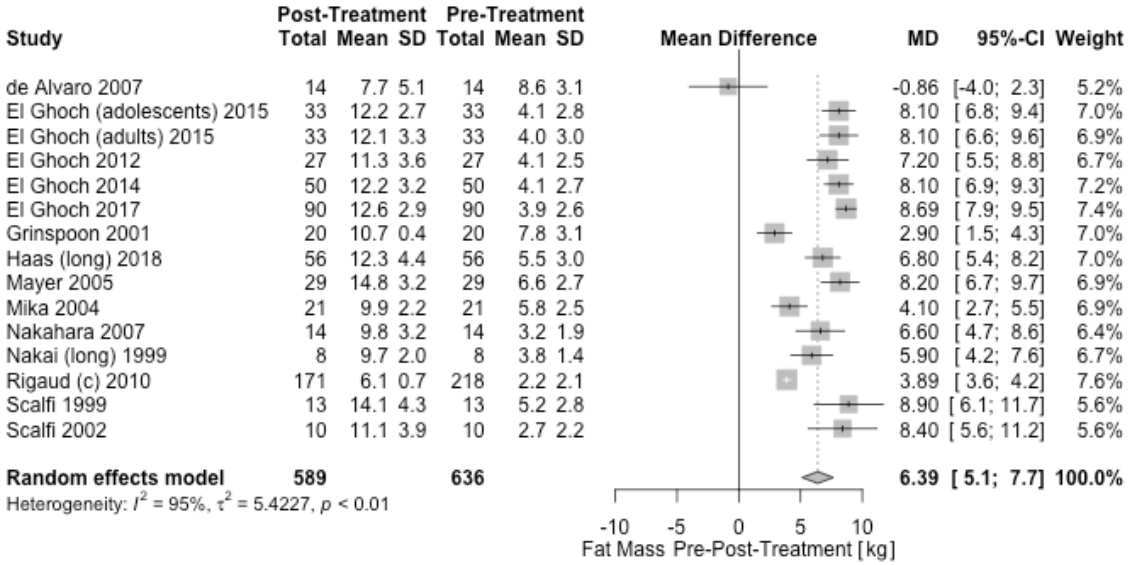

Figure S57. Longitudinal meta-analysis of studies reporting fat mass in female anorexia nervosa patients pre- and post-treatment. Fifteen samples had the appropriate data for the meta-analysis with 589 AN cases and 636 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 6.39 kg; 95% CI: 5.13, 7.65; P = 2.79 x 10^{-23}) with the mean differences ranging from -0.86 kg to 8.90 kg. Heterogeneity between studies was statistically highly significant (τ^2 = 5.42; P = 7.66 x 10^{-49}; I^2 = 95.0%). C, subtype-combined sample.

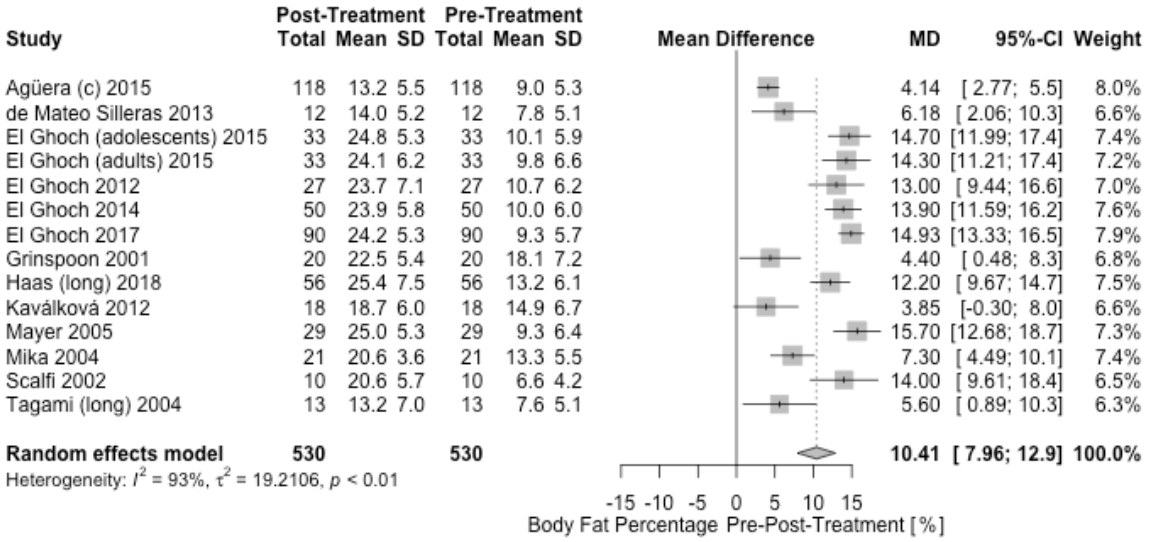

Figure S58. Longitudinal meta-analysis of studies reporting body fat percentage in female anorexia nervosa patients pre- and post-treatment. Fourteen samples had the appropriate data for the meta-analysis with 530 AN cases and 530 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 10.4%; 95% CI: 7.96, 12.87; $P = 9.23 \times 10^{-17}$) with the mean differences ranging from 3.9% to 15.7%. Heterogeneity between studies was statistically highly significant ($\tau^2 = 19.21$; $P = 2.07 \times 10^{-32}$; $I^2 = 93.0\%$). C, subtype-combined sample; long, longitudinal.

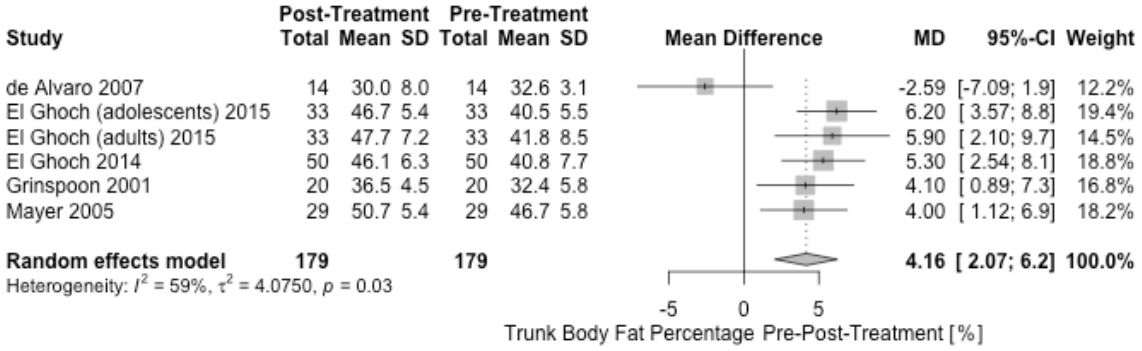

Figure S59. Longitudinal meta-analysis of studies reporting trunk body fat percentage in female anorexia nervosa patients pre- and post-treatment. Six samples had the appropriate data for the meta-analysis with 179 AN cases and 179 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 4.2%; 95% CI: 2.07, 6.25; $P = 9.67 \times 10^{-5}$) with the mean differences ranging from -2.6% to 6.2%. Heterogeneity between studies was statistically significant ($\tau^2 = 4.08$; $P = 0.03$; $I^2 = 59.0\%$).

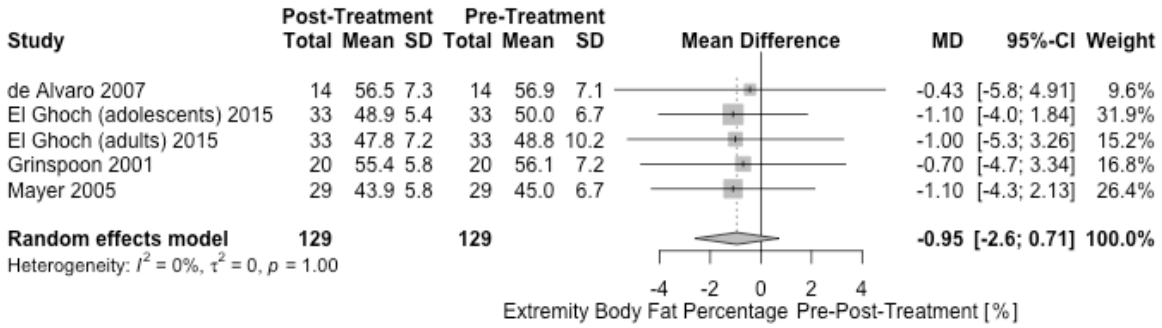

Figure S60. Longitudinal meta-analysis of studies reporting extremity body fat percentage in female anorexia nervosa patients pre- and post-treatment. Five samples had the appropriate data for the meta-analysis with 129 AN cases and 129 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -1.0%; 95% CI: -2.61, 0.71; P = 0.26) with the mean differences ranging from -1.1% to -0.4%. There was no Heterogeneity between studies (τ^2 = 0.00; P = 1.00; I^2 = 0.0%).

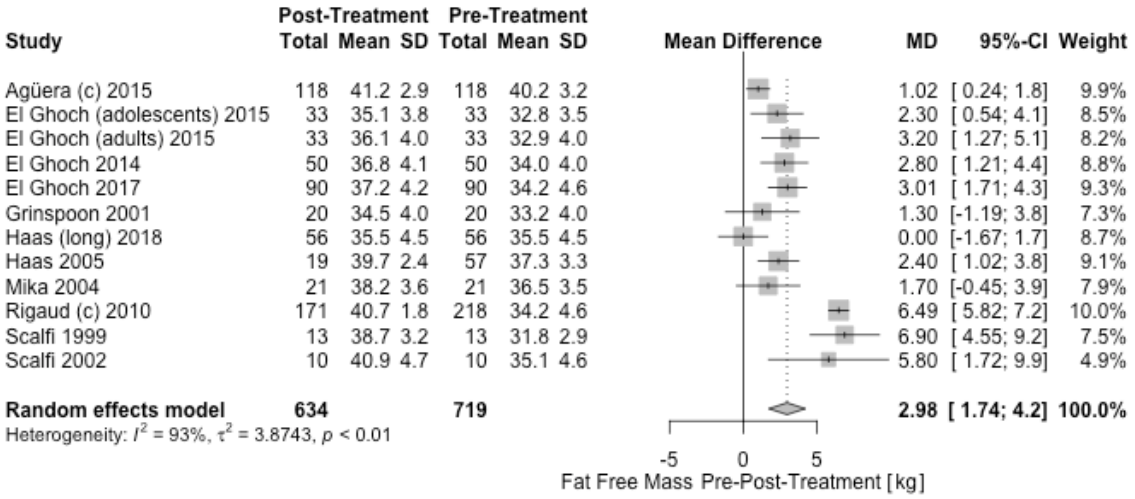

Figure S61. Longitudinal meta-analysis of studies reporting fat free mass in female anorexia nervosa patients pre- and post-treatment. Twelve samples had the appropriate data for the meta-analysis with 634 AN cases and 719 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 2.98 kg; 95% CI: 1.74, 4.22; P = 2.35 x 10^{-6}) with the mean differences ranging from 0.00 kg to 6.90 kg. Heterogeneity between studies was statistically highly significant (τ^2 = 3.87; P = 4.57x 10^{-27}; I^2 = 93.0%). C, subtype-combined sample.

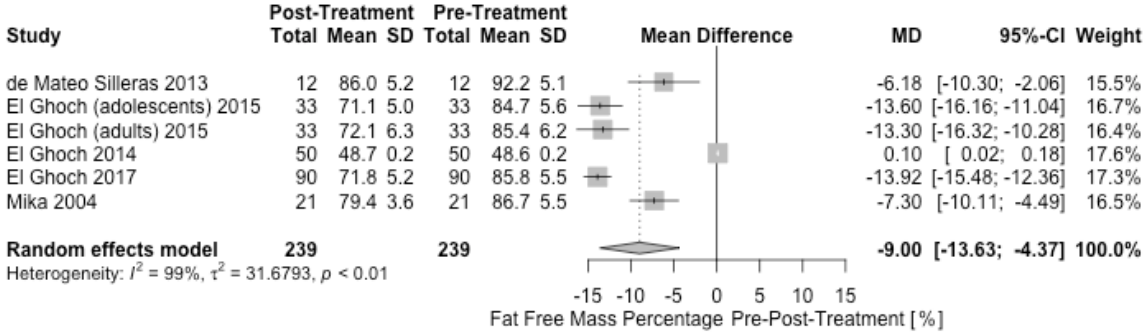

Figure S62. Longitudinal meta-analysis of studies reporting fat free mass percentage in female anorexia nervosa patients pre- and post-treatment. Six samples had the appropriate data for the meta-analysis with 239 AN cases and 239 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -9.0%; 95% CI: -13.6, -4.4; $P = 1.38 \times 10^{-4}$) with the mean differences ranging from -13.9% to 0.1%. Heterogeneity between studies was statistically highly significant ($\tau^2 = 31.68$; $P = 9.94 \times 10^{-112}$; $I^2 = 99.0\%$).

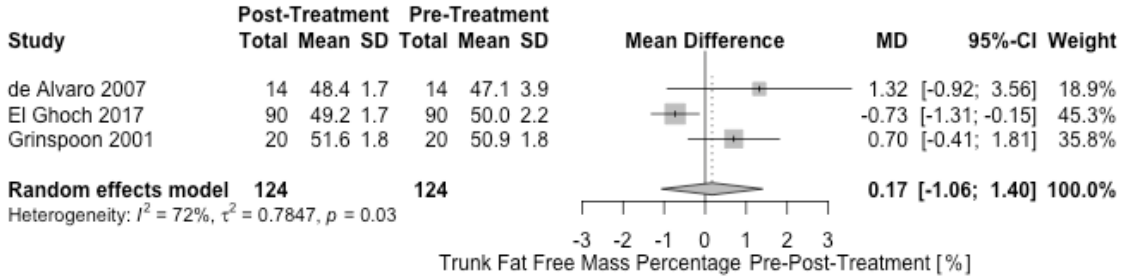

Figure S63. Longitudinal meta-analysis of studies reporting trunk fat free mass percentage in female anorexia nervosa patients pre- and post-treatment. Three samples had the appropriate data for the meta-analysis with 124 AN cases and 124 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 0.2%; 95% CI: -1.1, 1.4; $P = 0.79$) with the mean differences ranging from -0.7% to 1.3%. Heterogeneity between studies was statistically significant ($\tau^2 = 0.78$; $P = 0.03$; $I^2 = 72.3\%$).

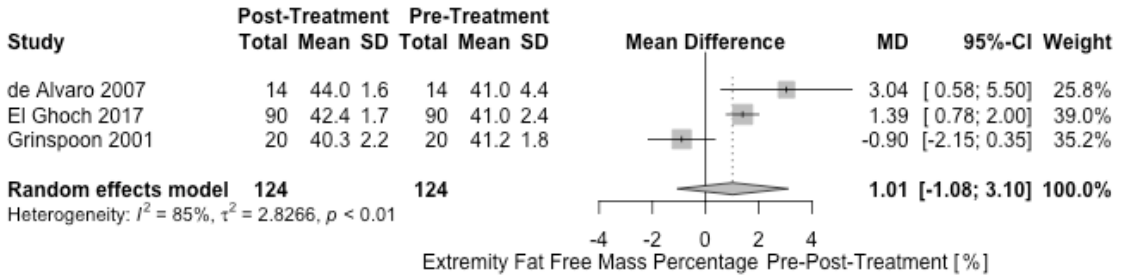

Figure S64. Longitudinal meta-analysis of studies reporting extremity fat free mass percentage in female anorexia nervosa patients pre- and post-treatment. Three samples had the appropriate data for the meta-analysis with 124 AN cases and 124 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 1.0%; 95% CI: -1.08, 3.10; $P = 0.34$) with the mean differences ranging from -0.9% to 3.0%. Heterogeneity between studies was statistically significant ($\tau^2 = 2.83$; $P = 1.51 \times 10^{-3}$; $I^2 = 84.6\%$).

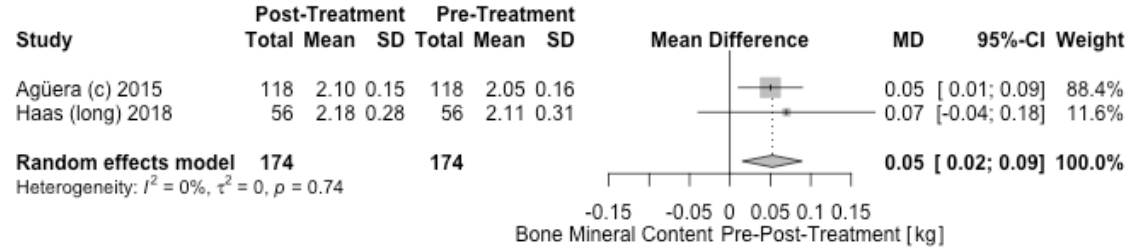

Figure S65. Longitudinal meta-analysis of studies reporting bone mineral content in female anorexia nervosa patients pre- and post-treatment. Two samples had the appropriate data for the meta-analysis with 174 AN cases and 174 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 0.05 kg; 95% CI: 0.02, 0.09; $P = 5.86 \times 10^{-3}$) with the mean differences ranging from 0.05 kg to 0.07 kg. There was no Heterogeneity between studies ($\tau^2 = 0.00$; $P = 0.74$; $I^2 = 0.0\%$). C, subtype-combined sample; long, longitudinal.

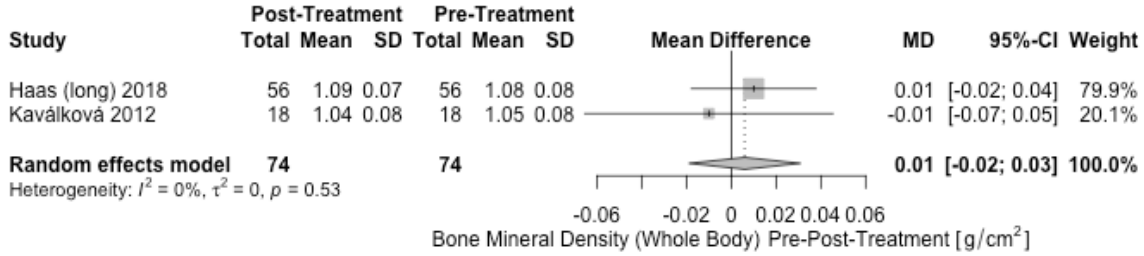

Figure S66. Longitudinal meta-analysis of studies reporting bone mineral density (whole body) in female anorexia nervosa patients pre- and post-treatment. Two samples had the appropriate data for the meta-analysis with 74 AN cases and 74 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 0.01 g/cm^2; 95% CI: -0.02, 0.03; $P = 0.64$) with the mean differences ranging from -0.01 g/cm^2 to 0.01 g/cm^2. There was no Heterogeneity between studies ($\tau^2 = 0.00$; $P = 0.53$; $I^2 = 0.0\%$). Long, longitudinal.

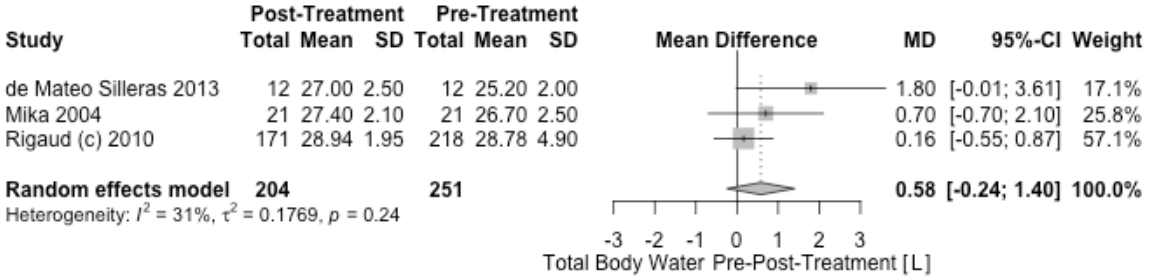

Figure S67. Longitudinal meta-analysis of studies reporting total body water in female anorexia nervosa patients pre- and post-treatment. Three samples had the appropriate data for the meta-analysis with 204 AN cases and 251 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 0.58 L; 95% CI: -0.24, 1.40; $P = 0.17$) with the mean differences ranging from 0.16 L to 1.80 L. Heterogeneity between studies was not statistically significant ($\tau^2 = 0.18$; $P = 0.24$; $I^2 = 30.8\%$). C, subtype-combined sample.

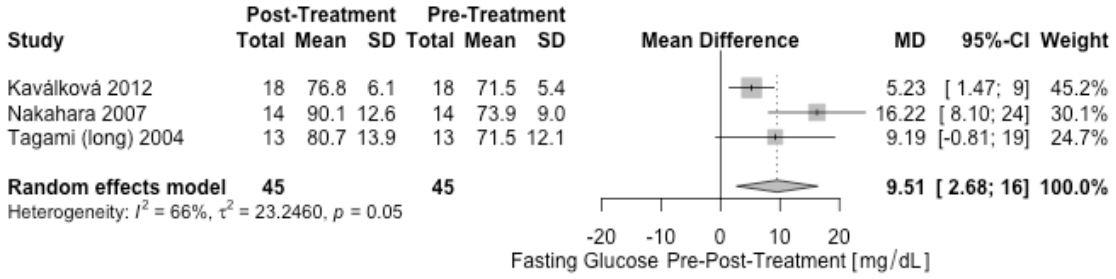

Figure S68. Longitudinal meta-analysis of studies reporting fasting glucose in female anorexia nervosa patients pre- and post-treatment. Three samples had the appropriate data for the meta-analysis with 45 AN cases and 45 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 9.51 mg/dL; 95% CI: 2.68, 16.35; $P = 6.38 \times 10^{-3}$) with the mean differences ranging from 5.23 mg/dL to 16.22 mg/dL. Heterogeneity between studies was statistically significant (τ^2 = 23.25; P = 0.05; I^2 = 66.3%). Long, longitudinal.

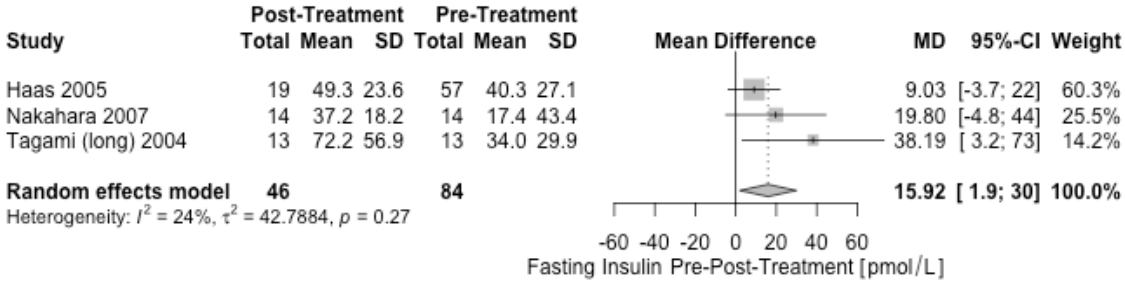

Figure S69. Longitudinal meta-analysis of studies reporting fasting insulin in female anorexia nervosa patients pre- and post-treatment. Three samples had the appropriate data for the meta-analysis with 45 AN cases and 45 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 15.92 pmol/L; 95% CI: 1.89, 29.95; P = 0.03) with the mean differences ranging from 9.03 pmol/L to 38.19 pmol/L. Heterogeneity between studies was not statistically significant (τ^2 = 42.79; P = 0.27) or large in magnitude (I^2 = 24.2%). Long, longitudinal.

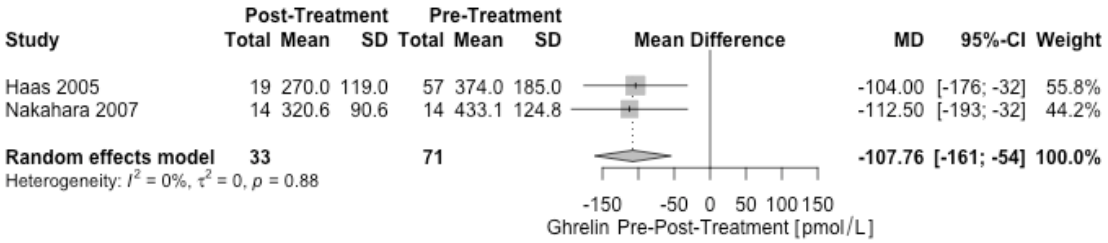

Figure S70. Longitudinal meta-analysis of studies reporting ghrelin in female anorexia nervosa patients pre- and post-treatment. Two samples had the appropriate data for the meta-analysis with 33 AN cases and 71 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -107.76 pmol/L; 95% CI: -161.47, -54.05; $P = 8.41 \times 10^{-5}$) with the mean differences ranging from -112.50 pmol/L to -104.00 pmol/L. There was no Heterogeneity between studies (τ^2 = 0.00; P = 0.88; I^2 = 0.0%).

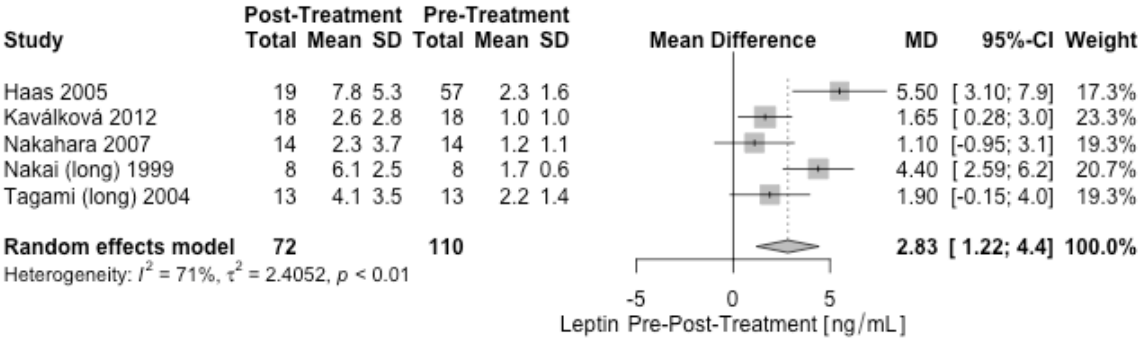

Figure S71. Longitudinal meta-analysis of studies reporting leptin in female anorexia nervosa patients pre- and post-treatment. Five samples had the appropriate data for the meta-analysis with 72 AN cases and 110 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 2.83 ng/mL; 95% CI: 1.22, 4.44; P = 5.79 x 10^{-4}) with the mean differences ranging from 1.10 ng/mL to 5.50 ng/mL. Heterogeneity between studies was not statistically significant (τ^2 = 2.41; P = 8.06 x 10^{-3}; I^2 = 71.0%). Long, longitudinal.

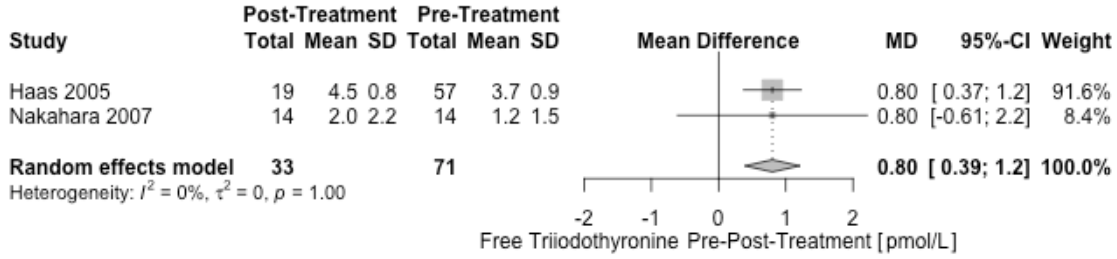

Figure S72. Longitudinal meta-analysis of studies reporting free triiodothyronine in female anorexia nervosa patients pre- and post-treatment. Two samples had the appropriate data for the meta-analysis with 33 AN cases and 71 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 0.80 pmol/L; 95% CI: 0.39, 1.21; P = 1.33 x 10^{-4}) with the mean differences ranging from 0.80 pmol/L to 0.80 pmol/L. There was no Heterogeneity between studies (τ^2 = 0.00; P = 1.00; I^2 = 0.0%).

2.8 Cross-sectional meta-analyses of studies comparing weight-recovered anorexia nervosa patients with healthy controls

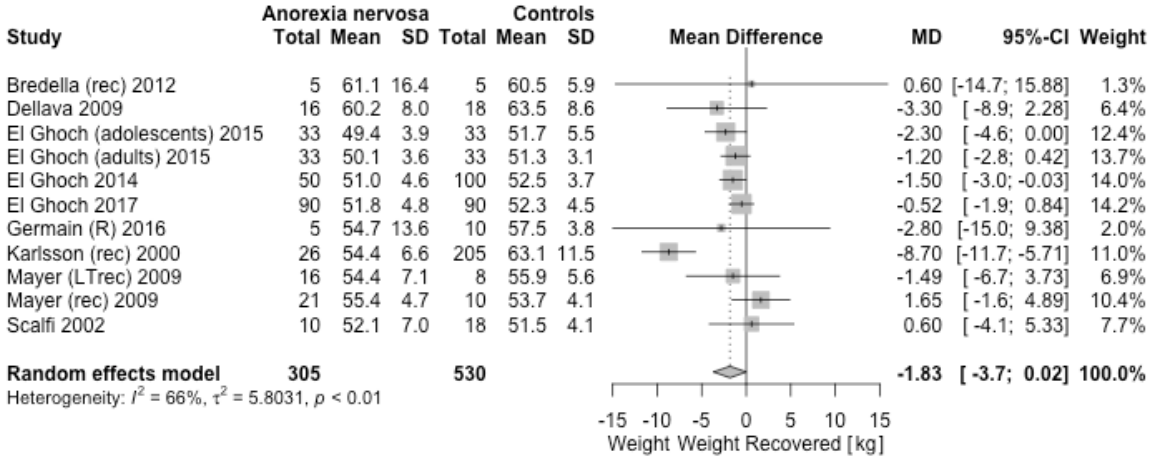

Figure S73. Cross-sectional meta-analysis of studies reporting <u>weight</u> in weight-recovered female anorexia nervosa patients compared with healthy controls. Eleven samples had the appropriate data for the meta-analysis with 305 AN cases and 530 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -1.83 kg; 95% CI: -3.68, 0.02; P = 0.05) with the mean differences ranging from -8.70 kg to 1.65 kg. Heterogeneity between studies was statistically significant (τ^2 = 5.80; P = 9.43 x 10^{-4}; I^2 = 66.4%). C, subtype-combined sample; rec, recovered; LTrec, long term weight-recovered.

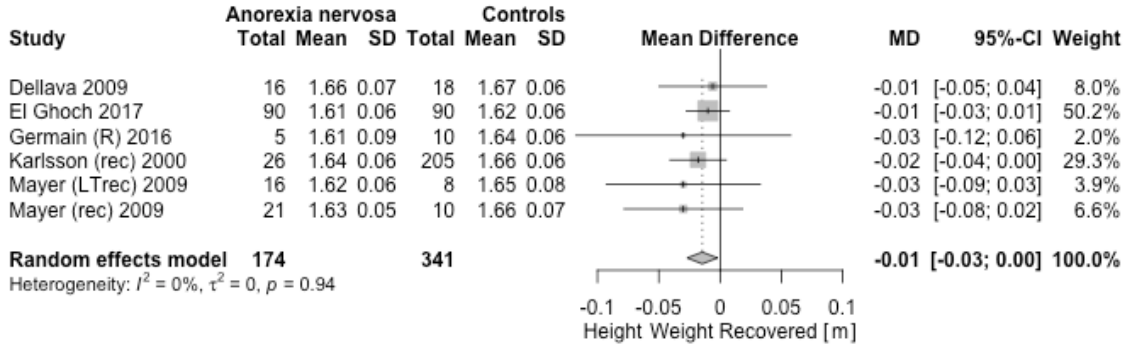

Figure S74. Cross-sectional meta-analysis of studies reporting <u>height</u> in weight-recovered female anorexia nervosa patients compared with healthy controls. Six samples had the appropriate data for the meta-analysis with 174 AN cases and 341 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.01 m; 95% CI: -0.03, 0.00; P = 0.02) with the mean differences ranging from -0.03 m to -0.01 m. There was no Heterogeneity between studies (τ^2 = 0.00; P = 0.94; I^2 = 0.0%). R, restricting; Rec, weight-recovered; LTrec, long term weight-recovered.

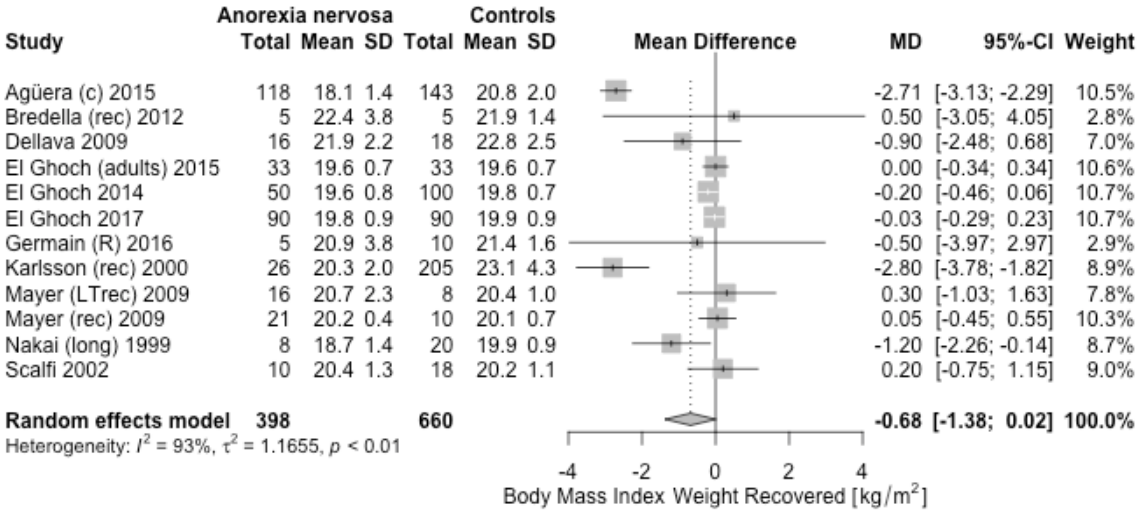

Figure S75. Cross-sectional meta-analysis of studies reporting body mass index in weight-recovered female anorexia nervosa patients compared with healthy controls. Twelve samples had the appropriate data for the meta-analysis with 398 AN cases and 660 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.68 kg/m^2; 95% CI: -1.38, 0.02; P = 6.76 x 10^{-3}) with the mean differences ranging from -2.80 kg/m^2 to 0.50 kg/m^2. Heterogeneity between studies was statistically highly significant (τ^2 = 1.17; P = 1.16 x 10^{-29}; I^2 = 93.3%). C, subtype-combined sample; long, longitudinal; rec, weight-recovered; LTrec, long term weight-recovered.

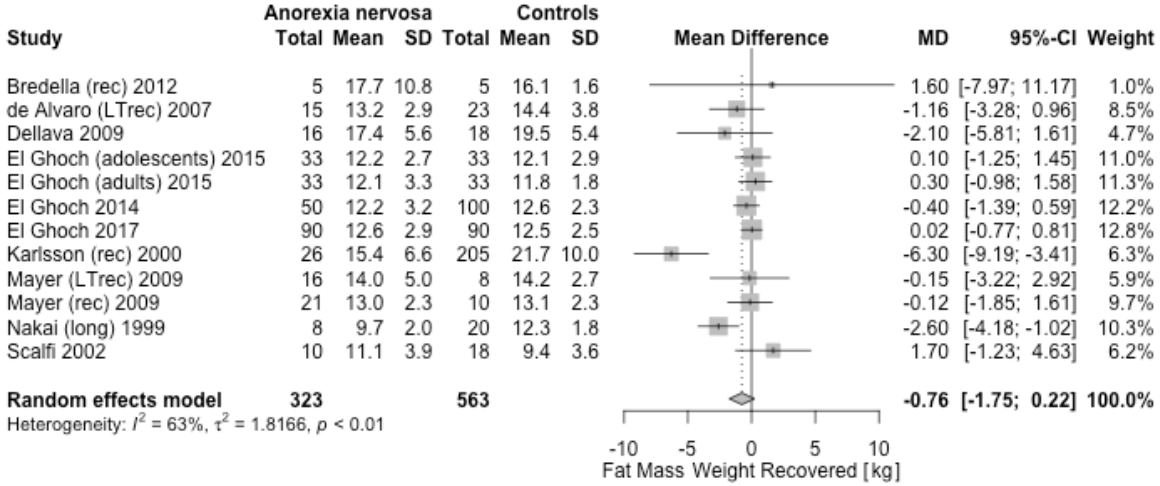

Figure S76. Cross-sectional meta-analysis of studies reporting fat mass in weight-recovered female anorexia nervosa patients compared with healthy controls. Twelve samples had the appropriate data for the meta-analysis with 323 AN cases and 563 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.76 kg; 95% CI: -1.75, 0.22; P = 013) with the mean differences ranging from -6.30 kg to 1.70 kg. Heterogeneity between studies was statistically significant (τ^2 =

1.82; P = 0.00; I^2 = 63.0%). Long, longitudinal; rec, weight-recovered; LTrec, long term weight-recovered.

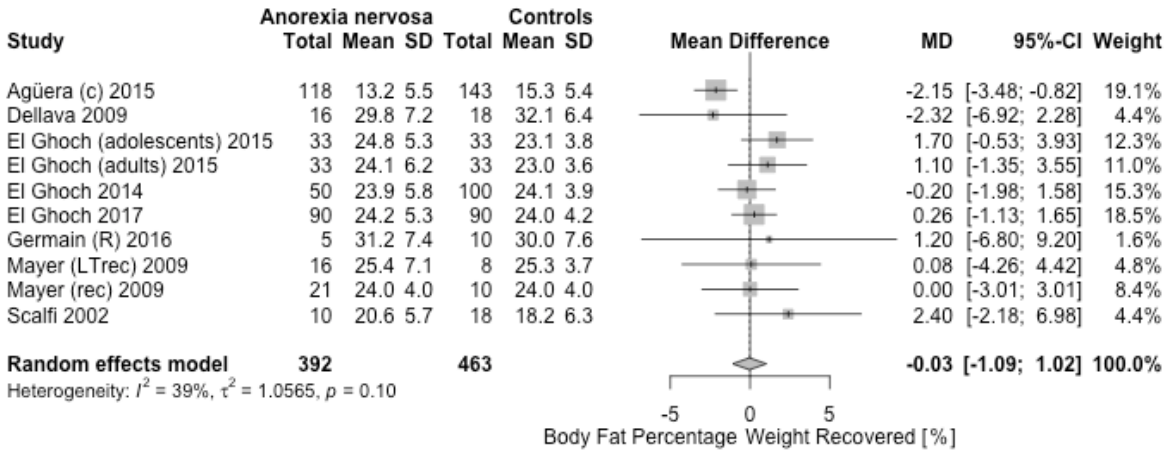

Figure S77. Cross-sectional meta-analysis of studies reporting body fat percentage in weight-recovered female anorexia nervosa patients compared with healthy controls. Ten samples had the appropriate data for the meta-analysis with 392 AN cases and 463 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.03%; 95% CI: -1.09, 1.02; P = 0.95) with the mean differences ranging from -2.32% to 2.40%. Heterogeneity between studies was not statistically significant (τ^2 = 1.06; P = 0.10) or large in magnitude (I^2 = 39.0%). C, subtype-combined sample; rec, weight-recovered, LTrec, long term weight-recovered.

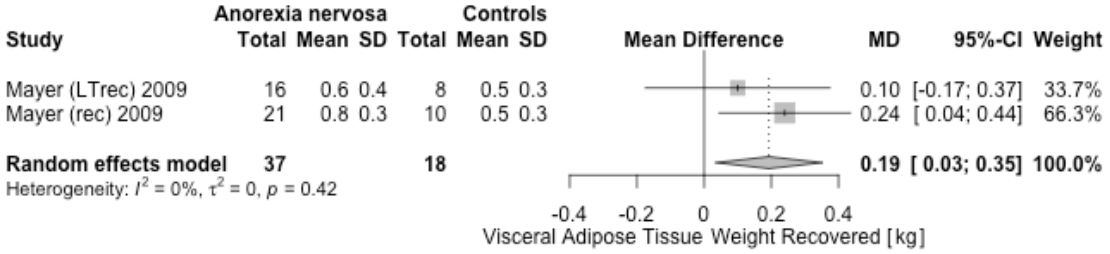

Figure S78. Cross-sectional meta-analysis of studies reporting visceral adipose tissue in weight-recovered female anorexia nervosa patients compared with healthy controls. Two samples had the appropriate data for the meta-analysis with 37 AN cases and 18 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 0.19 kg; 95% CI: 0.03, 0.35; P = 0.02) with the mean differences ranging from 0.10 kg to 0.24 kg. There was no Heterogeneity between studies (τ^2 = 0.00; P = 0.42; I^2 = 0.0%). Rec, weight-recovered; LTrec, long term weight-recovered.

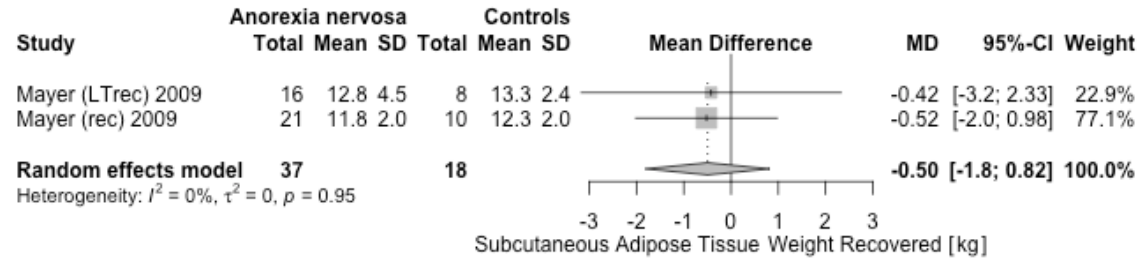

Figure S79. Cross-sectional meta-analysis of studies reporting subcutaneous adipose tissue in weight-recovered female anorexia nervosa patients compared with healthy controls. Two samples had the appropriate data for the meta-analysis with 37 AN cases and 18 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.50 kg; 95% CI: -1.81, 0.82; P = 0.46) with the mean differences ranging from -0.52 kg to -0.42 kg. There was no Heterogeneity between studies (τ^2 = 0.00; P = 0.95; I^2 = 0.0%). Rec, weight-recovered; LTrec, long term weight-recovered.

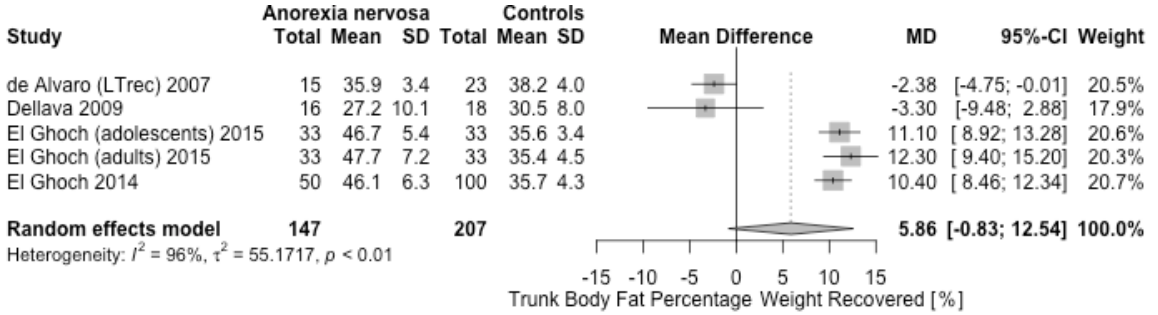

Figure S80. Cross-sectional meta-analysis of studies reporting trunk body fat percentage in weight-recovered female anorexia nervosa patients compared with healthy controls. Five samples had the appropriate data for the meta-analysis with 147 AN cases and 207 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 5.9%; 95% CI: -0.83, 12.54; P = 0.09) with the mean differences ranging from -3.3% to 12.3%. Heterogeneity between studies was statistically highly significant (τ^2 = 55.17; P = 1.75 x 10^{-22}; I^2 = 96.3%). LTrec, long term weight-recovered.

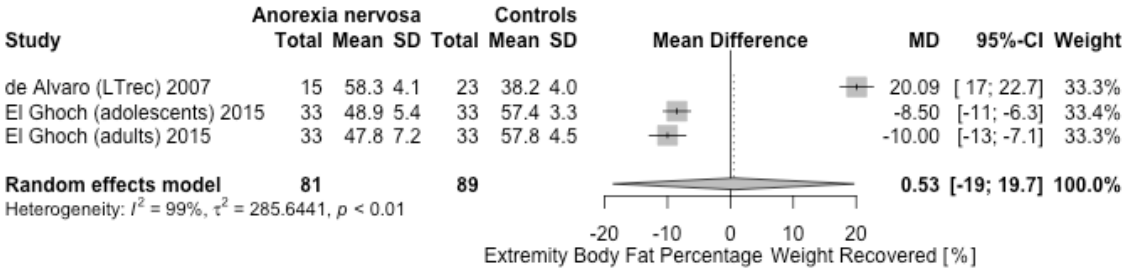

Figure S81. Cross-sectional meta-analysis of studies reporting extremity body fat percentage in weight-recovered female anorexia nervosa patients compared with healthy controls. Three samples had the appropriate data for the meta-analysis with 81 AN cases and 89 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 0.5%; 95% CI: -18.65, 19.71; P = 0.96) with the mean differences ranging from -10.0% to 20.%. Heterogeneity between studies was statistically highly significant (τ^2 = 285.64; P = 7.45 x 10^{-72}; I^2 = 99.4%). LTrec, long term weight-recovered.

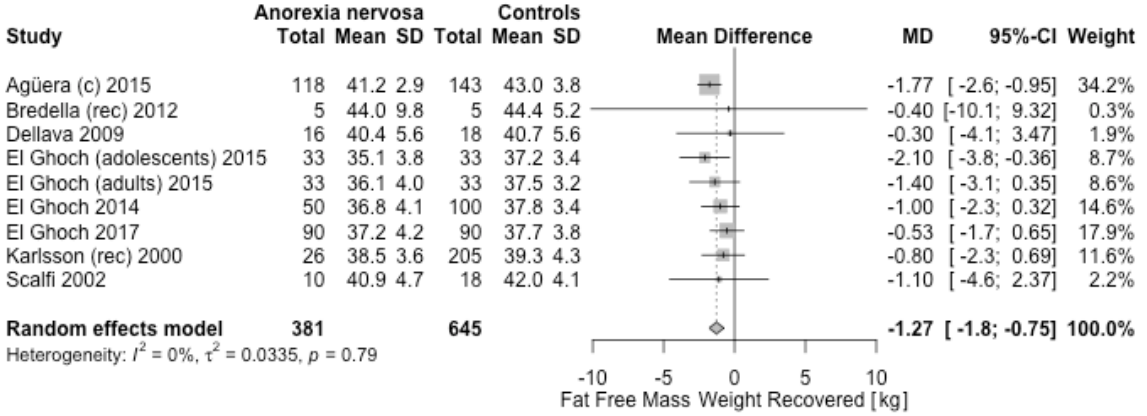

Figure S82. Cross-sectional meta-analysis of studies reporting fat free mass in weight-recovered female anorexia nervosa patients compared with healthy controls. Nine samples had the appropriate data for the meta-analysis with 381 AN cases and 645 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -1.27 kg; 95% CI: -1.80, -0.75; $P = 1.81 \times 10^{-6}$) with the mean differences ranging from -2.10 kg to -0.30 kg. There was no Heterogeneity between studies ($\tau^2 = 0.03$; $P = 0.79$; $I^2 = 0.0\%$). C, subtype-combined sample; rec, weight-recovered.

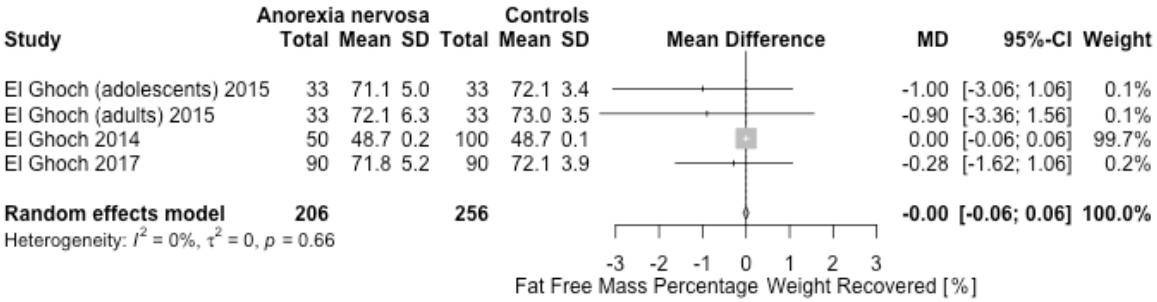

Figure S83. Cross-sectional meta-analysis of studies reporting fat free mass percentage in weight-recovered female anorexia nervosa patients compared with healthy controls. Four samples had the appropriate data for the meta-analysis with 206 AN cases and 256 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.0%; 95% CI: -0.06, 0.06; $P = 0.95$) with the mean differences ranging from -1.0% to 0.0%. There was no Heterogeneity between studies ($\tau^2 = 0.00$; $P = 0.66$; $I^2 = 0.0\%$).

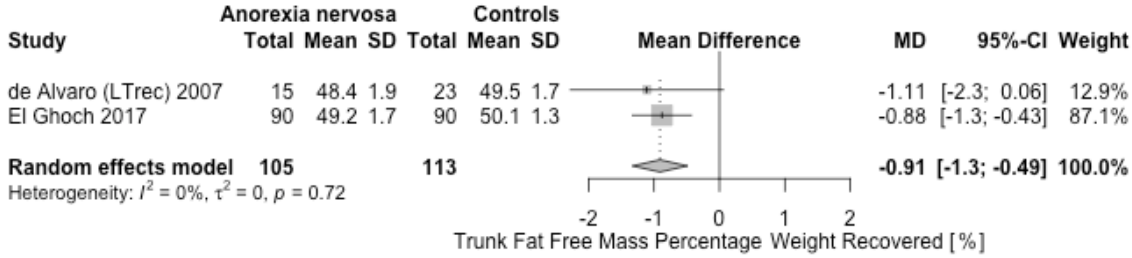

Figure S84. Cross-sectional meta-analysis of studies reporting trunk fat free mass percentage in weight-recovered female anorexia nervosa patients compared with healthy controls. Two samples had the appropriate data for the meta-analysis with 105 AN cases and 113 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.9%; 95% CI: -1.33, -0.49; $P = 2.29 \times 10^{-5}$) with the mean differences ranging from -1.1% to -0.9%. There was no Heterogeneity between studies ($\tau^2 = 0.00$; $P = 0.72$; $I^2 = 0.0\%$). LTrec, long term weight-recovered.

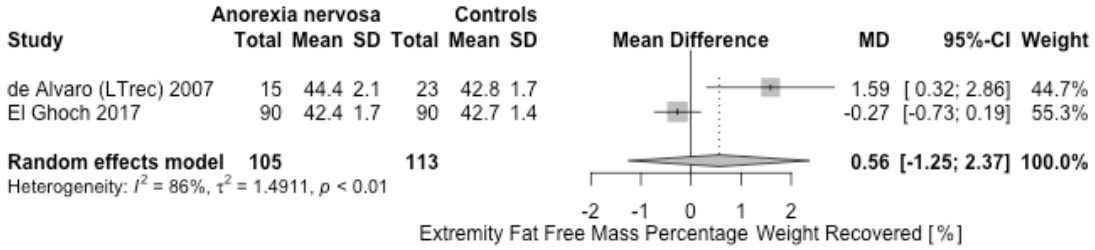

Figure S85. Cross-sectional meta-analysis of studies reporting extremity fat free mass percentage in weight-recovered female anorexia nervosa patients compared with healthy controls. Two samples had the appropriate data for the meta-analysis with 105 AN cases and 113 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: 0.6%; 95% CI: -1.25, 2.37; $P = 0.54$) with the mean differences ranging from -0.3% to 1.6%. Heterogeneity between studies was statistically significant ($\tau^2 = 1.49$; $P = 7.10 \times 10^{-3}$; $I^2 = 86.2\%$). LTrec, long term weight-recovered.

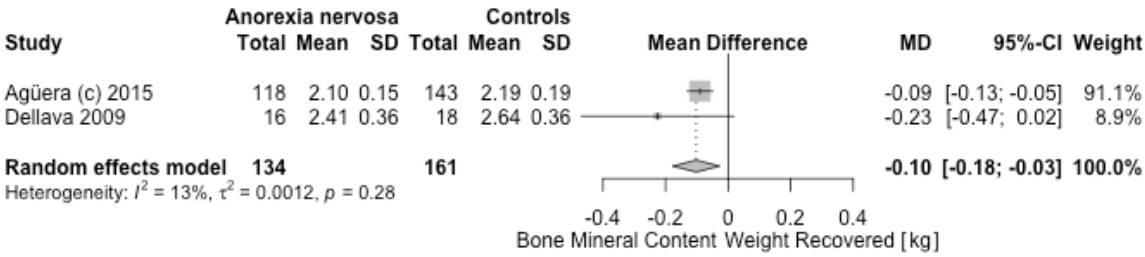

Figure S86. Cross-sectional meta-analysis of studies reporting bone mineral content in weight-recovered female anorexia nervosa patients compared with healthy controls. Two samples had the appropriate data for the meta-analysis with 134 AN cases and 161 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.10 kg; 95% CI: -0.18, -0.03; $P = 0.01$) with the mean differences ranging from -0.23 kg to -0.09 kg. There was no heterogeneity between studies ($\tau^2 = 0.00$; $P = 0.28$; $I^2 = 13.0\%$). C, subtype-combined sample.

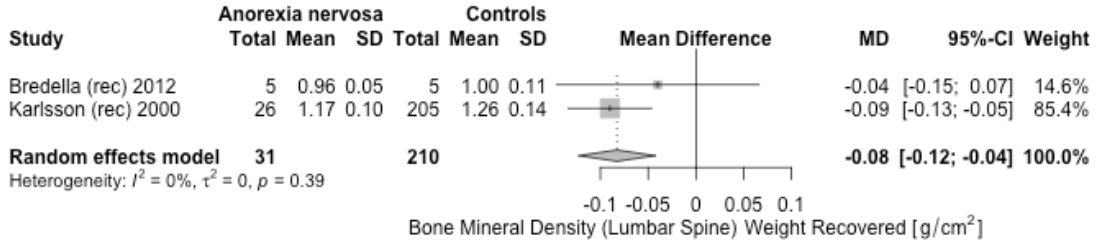

Figure S87. Cross-sectional meta-analysis of studies reporting bone mineral density (lumbar spine) in weight-recovered female anorexia nervosa patients compared with healthy controls. Two samples had the appropriate data for the meta-analysis with 31 AN cases and 210 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.08 g/cm^2; 95% CI: -0.12, -0.04; P = 6.28 x 10^{-5}) with the mean differences ranging from -0.09 g/cm^2 to -0.04 g/cm^2. There was no Heterogeneity between studies (τ^2 = 0.00; P = 0.39; I^2 = 0.0%). Rec, weight-recovered.

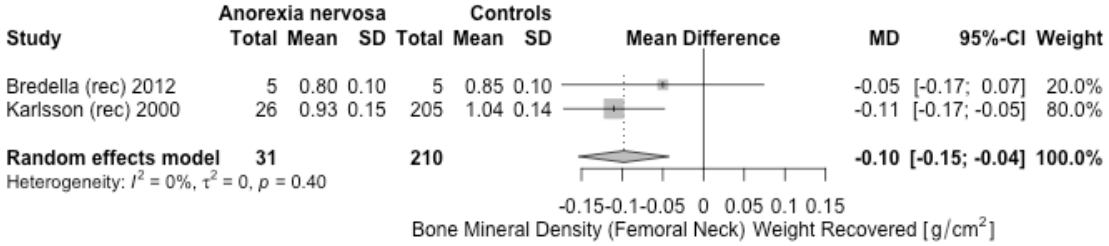

Figure S88. Cross-sectional meta-analysis of studies reporting bone mineral density (femoral neck) in weight-recovered female anorexia nervosa patients compared with healthy controls. Two samples had the appropriate data for the meta-analysis with 31 AN cases and 210 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.10 g/cm^2; 95% CI: -0.15, -0.04; P = 5.31 x 10^{-4}) with the mean differences ranging from -0.11 g/cm^2 to -0.05 g/cm^2. There was no Heterogeneity between studies (τ^2 = 0.00; P = 0.40; I^2 = 0.0%). Rec, weight-recovered.

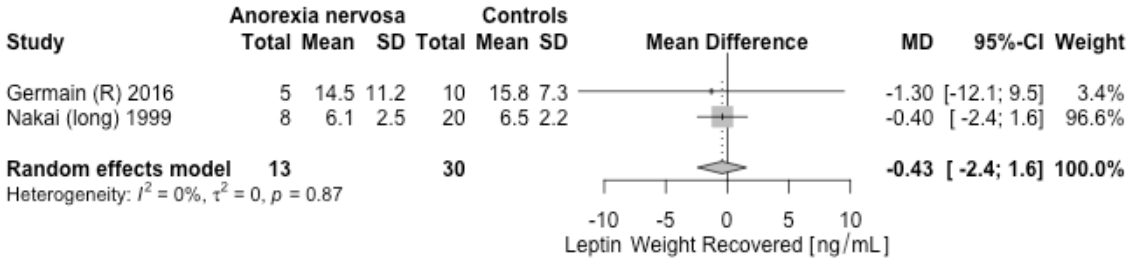

Figure S89. Cross-sectional meta-analysis of studies reporting leptin in weight-recovered female anorexia nervosa patients compared with healthy controls. Two samples had the appropriate data for the meta-analysis with 13 AN cases and 30 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.43 ng/mL; 95% CI: -2.41, 1.55; P = 0.67) with the mean differences ranging from -1.30 ng/mL to -0.40 ng/mL. There was no heterogeneity between studies (τ^2 = 0.00; P = 0.87; I^2 = 0.0%). Long, longitudinal R, restricting.

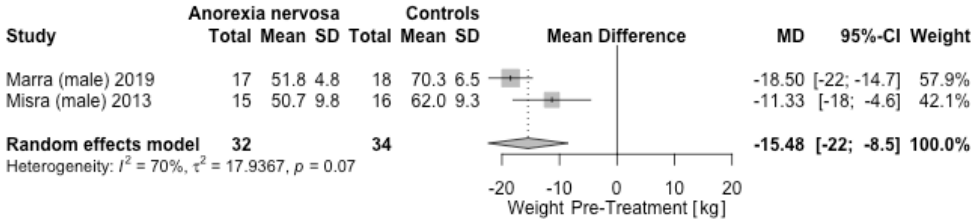

Figure S90. Cross-sectional meta-analysis of studies reporting weight in acutely-ill/pre-treatment male anorexia nervosa patients compared with healthy controls. Two samples had the appropriate data for the meta-analysis with 32 AN cases and 34 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -15.48 kg; % CI: -22.42, -8.54; $P = 1.22 \times 10^{-5}$) with the mean differences ranging from -18.50 kg to -11.33 kg. Heterogeneity between studies was not statistically significant (τ^2 = 17.94; P = 0.07; I^2 = 69.80%).

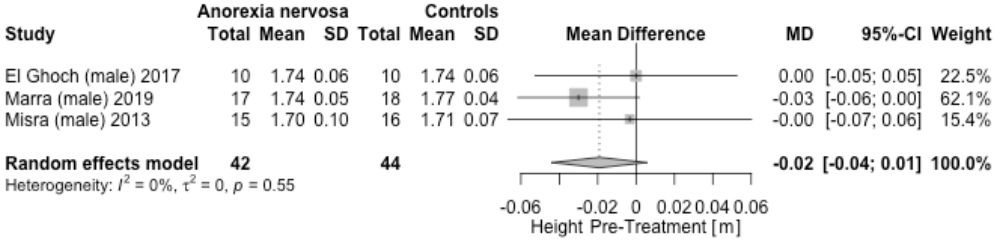

Figure S91. Cross-sectional meta-analysis of studies reporting height in acutely-ill/pre-treatment male anorexia nervosa patients compared with healthy controls. Three samples had the appropriate data for the meta-analysis with 42 AN cases and 44 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -0.02 m; 95% CI: -0.04, 0.01; P = 0.13) with the mean differences ranging from -0.03 m to 0.00 m. Heterogeneity between studies was not statistically significant (τ^2 = 0; P = 0.55; I^2 = 0%). C, subtype-combined sample.

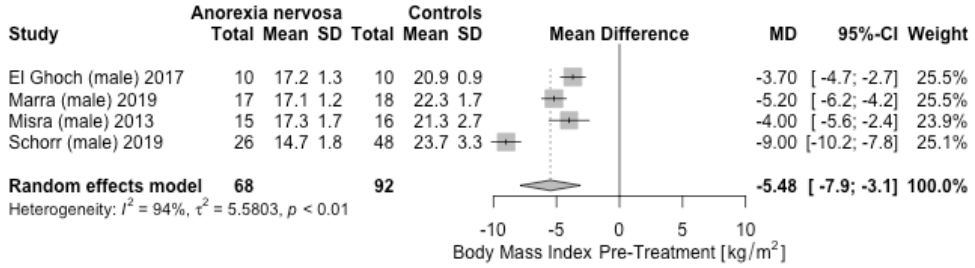

Figure S92. Cross-sectional meta-analysis of studies reporting body mass index in acutely-ill/pre-treatment male anorexia nervosa patients compared with healthy controls. Four samples had the appropriate data for the meta-analysis with 68 AN cases and 92 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -5.48 kg/m^2; 95% CI: -7.87, -3.09; $P = 6.92 \times 10^{-6}$) with the mean differences ranging from -9.00 kg/m^2 to -3.70 kg/m^2. Heterogeneity between studies was statistically highly significant (τ^2 = 5.58; $P = 3.65 \times 10^{-11}$; I^2 = 94.2%).

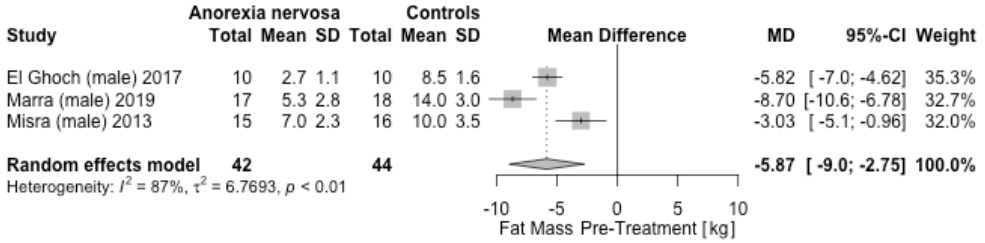

Figure S93. Cross-sectional meta-analysis of studies reporting fat mass in acutely-ill/pre-treatment male anorexia nervosa patients compared with healthy controls. Three samples had the appropriate data for the meta-analysis with 42 AN cases and 44 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -5.87 kg; 95% CI: -8.98, -2.75; $P = 2.22 \times 10^{-4}$) with the mean differences ranging from -8.70 kg to -3.03 kg. Heterogeneity between studies was statistically highly significant (τ^2 =6.77; $P = 4.17 \times 10^{-4}$; I^2 = 87.20%). C, subtype-combined sample.

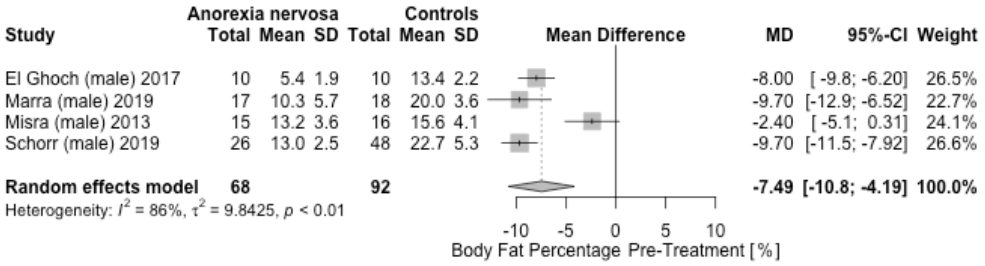

Figure S94. Cross-sectional meta-analysis of studies reporting body fat percentage in acutely-ill/pre-treatment male anorexia nervosa patients compared with healthy controls. Four samples had the appropriate data for the meta-analysis with 68 AN cases and 92 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -7.49%; 95% CI: -10.79, -4.19; $P = 8.76 \times 10^{-6}$) with the mean differences ranging from -9.70% to -2.40%. Heterogeneity between studies was statistically highly significant (τ^2 = 9.84; $P = 1.07 \times 10^{-4}$; I^2 = 85.70%). C, subtype-combined sample.

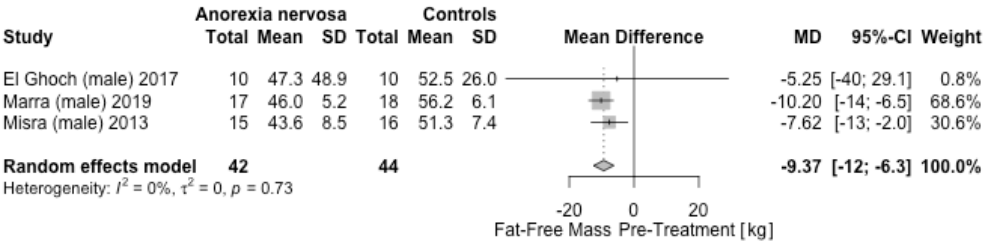

Figure S95. Cross-sectional meta-analysis of studies reporting fat-free mass in acutely-ill/pre-treatment male anorexia nervosa patients compared with healthy controls. Three samples had the appropriate data for the meta-analysis with 42 AN cases and 44 controls. A random-effects meta-analysis revealed a pooled estimate of the mean difference (MD: -9.37 kg; 95% CI: -12.47, -6.27; $P = 3.30 \times 10^{-9}$) with the mean differences ranging from -10.20 kg to -5.25 kg. Heterogeneity between studies was statistically highly significant (τ^2 = 0.00; P = 0.72; I^2 = 0%). C, subtype-combined sample.

2.9 Copas selection models: Adjustment for small study effects

9a) Bone mineral density (whole body) pre-treatment

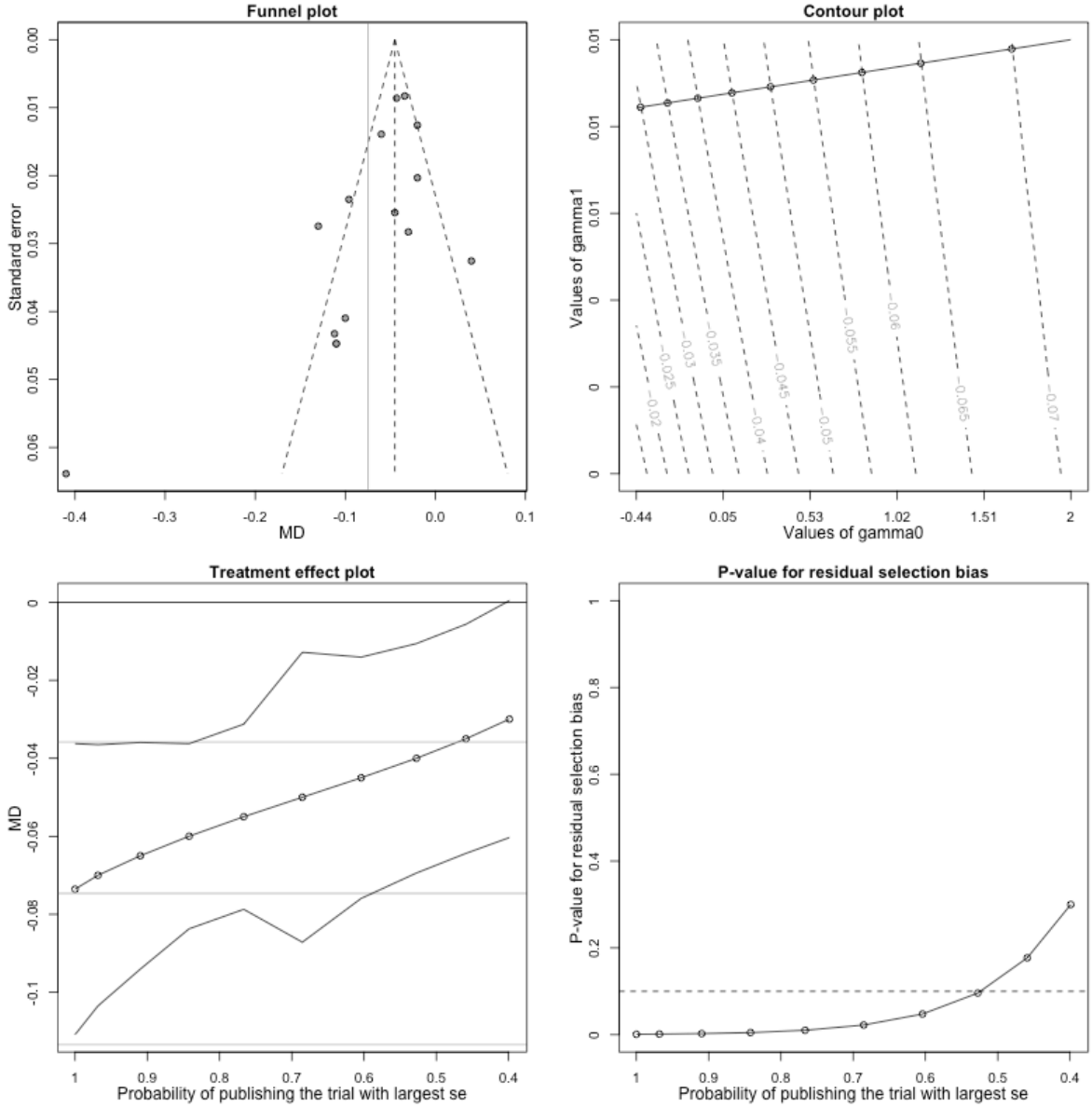

Figure S96. Copas model bone mineral density (whole body) pre-treatment
Figure S96a. Funnel plot for pre-treatment (acutely-ill AN) bone mineral density (whole body). The vertical gray line corresponds the random effects model estimate and the diagonal dashed lines correspond to ± 2 standard errors (SEs). If there is no heterogeneity and no publication bias, 95% of all studies should lie within the funnel.
Figure S96b. Contour plot. The plot shows the estimated treatment effect for a range of pairs ($\gamma 0$ and $\gamma 1$). The Copas selection model has two sensitivity parameters: $\gamma 0$ on the x-axis is roughly the probit of the probability that a study with a small sample size (large standard error, SE) is published and $\gamma 1$ on the y-axis is roughly the regression coefficient of the change in the probit of the probability that a study with observed precision 1/SE is published. The line of steepest descent from the top right corner descending to the left indicates selection. Contours in this plot should be smooth.

Figure S96c. Effect plot. The effect estimates highlighted in the contour plot (b) are also shown in this plot including their 95% confidence intervals. Values on the x-axis are calculated using the largest standard error (SE) of all studies in the given meta-analysis (the "smallest study") and values for $\gamma 0$ and $\gamma 1$ from the contour plot. Selection increases on the x-axis from the left to the right (because the probability of publishing the study with the largest SE decreases).

Figure S96d. P-value plot. The plot shows the p-value for residual selection bias. A p-value of p = 0.1 is regarded as significant indicated by the horizontal dashed line. If the contour of estimated effects crosses the dashed line, the adjusted effect can be read off at this point of selection.

The contour plot showed smooth contours with ranges for γ_0 and γ_1 being appropriate and the line orthogonal to the contours was well chosen (Figure 96b). The Copas model (i.e., maximum likelihood) estimate and its confidence interval with no publication bias (left hand end, solid line) agreed with the random effects estimate shown by the gray horizontal line. As the probability of publishing the smallest studies decreases the effect confidence intervals generally were getting narrower. The mean effect and its confidence intervals vary smoothly to the right of the area and the confidence intervals do not cut the null value (Figure 96c). The Copas model p-value for residual selection bias was significant with p = 0.001 and the relationship between the p-value for residual selection bias and the probability of publishing the smallest study (largest SE) was completely smooth indicating no local problems with the estimation. The Copas selection model analysis does not overturn the conclusion of the original meta-analysis comparing acutely-ill anorexia nervosa cases with healthy controls as the adjusted estimate of -0.03 g/cm^3 (95% CI, -0.06, -0.01; p = 0.02) with an estimated selection probability of 46% and 11 potentially unpublished studies is halved compared with the random effects model estimate with -0.07 g/cm^3 (95% CI, -0.11, -0.04) and has narrower confidence intervals. The point estimate was not contained in the original confidence interval.

9c) Fasting glucose pre-treatment

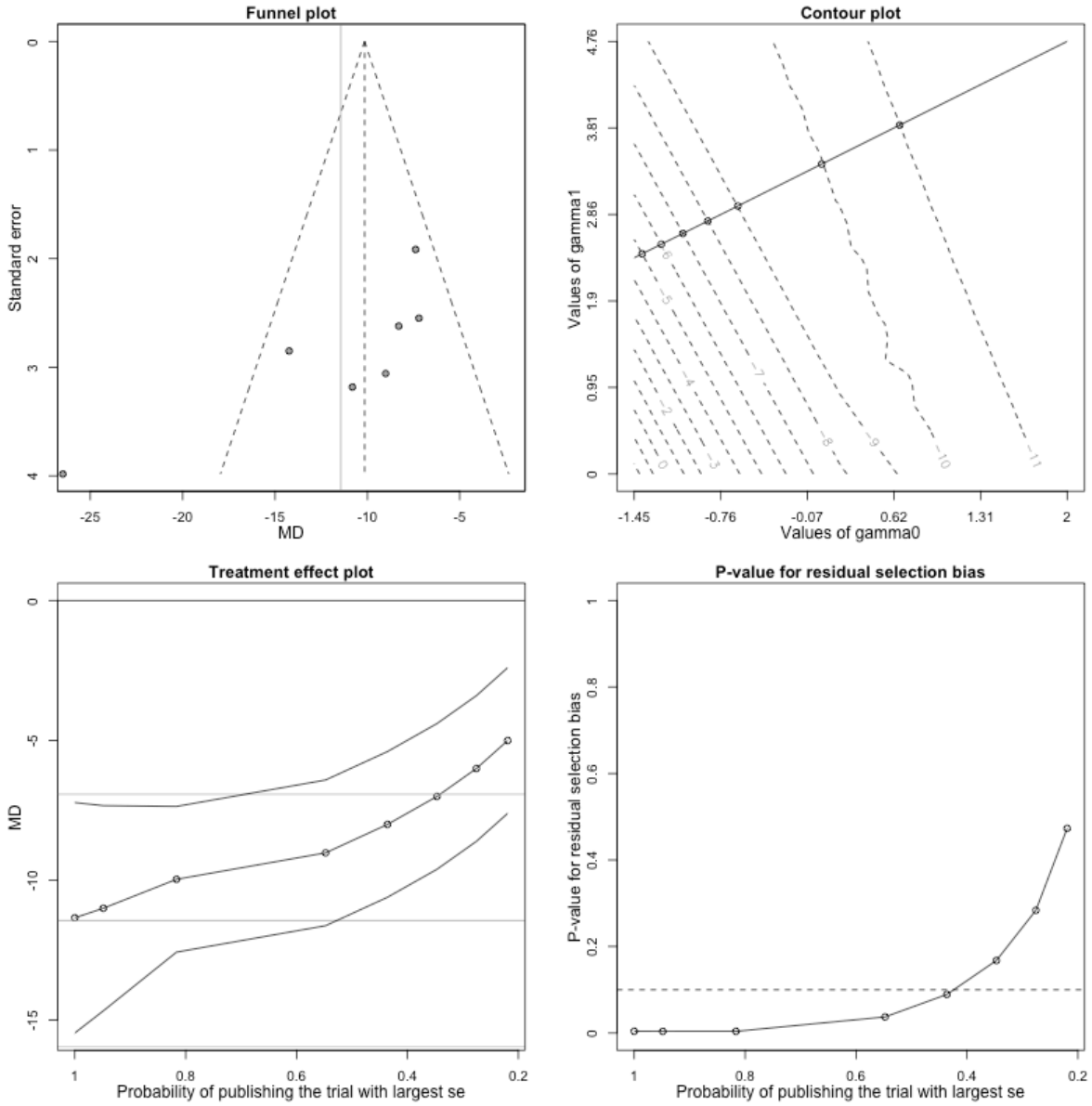

Figure S97. Copas model fasting glucose pre-treatment

Figure S97a. Funnel plot for pre-treatment (acutely-ill AN) fasting glucose. The vertical gray line corresponds the random effects model estimate and the diagonal dashed lines correspond to ± 2 standard errors (SEs). If there is no heterogeneity and no publication bias, 95% of all studies should lie within the funnel.

Figure S97b. Contour plot. The plot shows the estimated treatment effect for a range of pairs ($\gamma 0$ and $\gamma 1$). The Copas selection model has two sensitivity parameters: $\gamma 0$ on the x-axis is roughly the probit of the probability that a study with a small sample size (large standard error, SE) is published and $\gamma 1$ on the y-axis is roughly the regression coefficient of the change in the probit of the probability that a study with observed precision 1/SE is published. The line of steepest descent from the top right corner descending to the left indicates selection. Contours in this plot should be smooth.

Figure S97c. Effect plot. The effect estimates highlighted in the contour plot (b) are also shown in this plot including their 95% confidence intervals. Values on the x-axis are calculated using the largest standard error (SE) of all studies in the given meta-analysis

(the “smallest study”) and values for $\gamma 0$ and $\gamma 1$ from the contour plot. Selection increases on the x-axis from the left to the right (because the probability of publishing the study with the largest SE decreases).
Figure S97d. P-value plot. The plot shows the p-value for residual selection bias. A p-value of p = 0.1 is regarded as significant indicated by the horizontal dashed line. If the contour of estimated effects crosses the dashed line, the adjusted effect can be read off at this point of selection.

The contour plot showed smooth contours with ranges for γ_0 and γ_1 being appropriate and the line orthogonal to the contours was well chosen (Figure 97b). The Copas model (i.e., maximum likelihood) estimate and its confidence interval with no publication bias (left hand end, solid line) agreed with the random effects estimate shown by the gray horizontal line. As the probability of publishing the smallest studies decreases the effect confidence intervals generally were getting narrower. The mean effect and its confidence intervals vary smoothly to the right of the area and the confidence intervals do not cut the null value (Figure 97c). The Copas model p-value for residual selection bias was significant with p = 0.009 and the relationship between the p-value for residual selection bias and the probability of publishing the smallest study (largest SE) was completely smooth indicating no local problems with the estimation. The Copas selection model analysis does not overturn the conclusion of the original meta-analysis comparing acutely-ill anorexia nervosa cases with healthy controls as the adjusted estimate of -7.01 mg/dL (95% CI, -9.61, -4.40; p < 0.0001) with an estimated selection probability of 35% and 9 potentially unpublished studies is similar to the random effects model estimate with -11.44 mg/dL (95% CI, -15.95, -6.93) and has a comparable confidence interval. The adjusted point estimate has shrunken by a third and was contained in the original confidence interval.

9d) Leptin pre-treatment

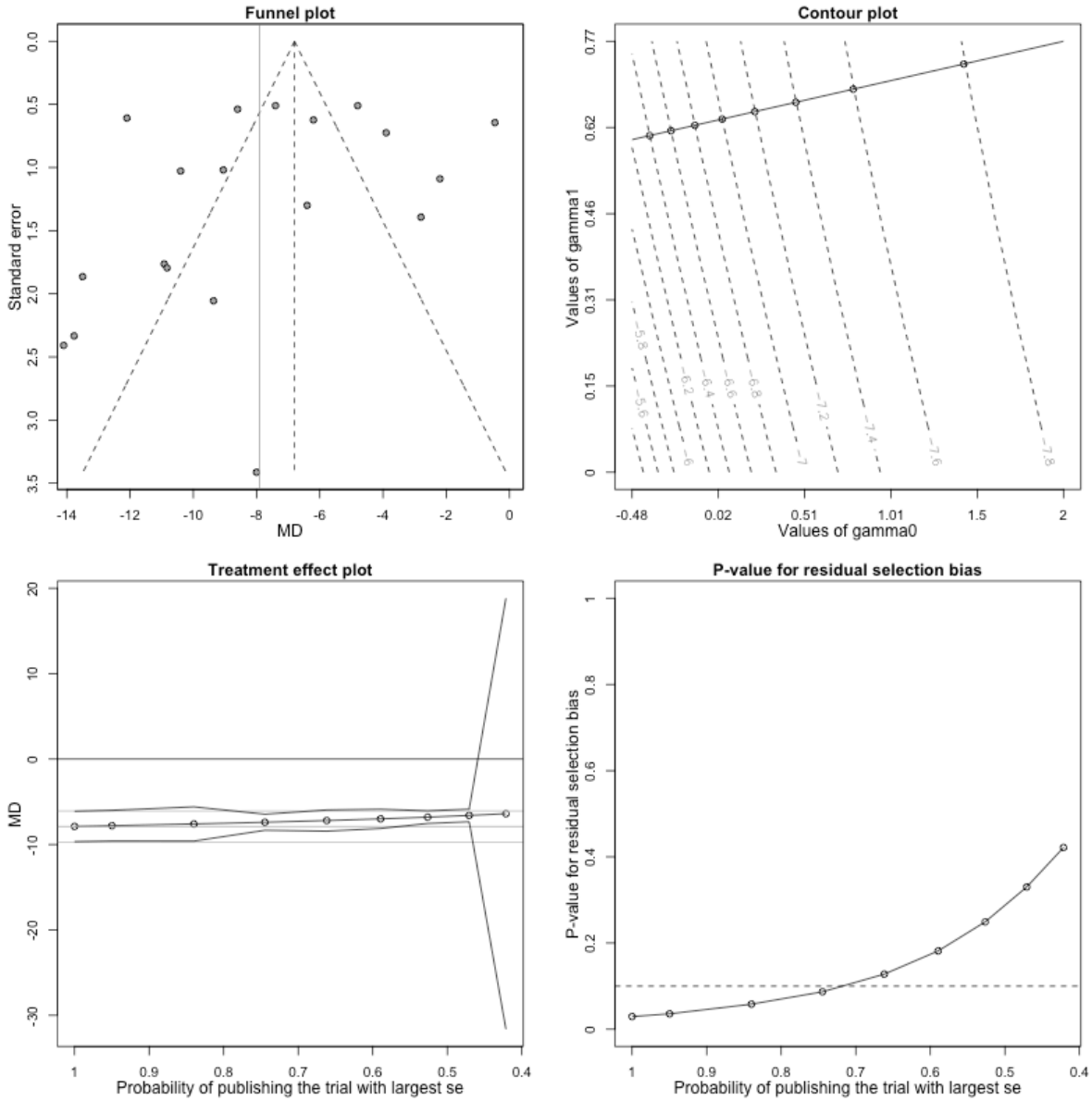

Figure S98. Copas model leptin pre-treatment

Figure S98a. Funnel plot for pre-treatment (acutely-ill AN) leptin. The vertical gray line corresponds the random effects model estimate and the diagonal dashed lines correspond to ± 2 standard errors (SEs). If there is no heterogeneity and no publication bias, 95% of all studies should lie within the funnel.

Figure S98b. Contour plot. The plot shows the estimated treatment effect for a range of pairs ($\gamma 0$ and $\gamma 1$). The Copas selection model has two sensitivity parameters: $\gamma 0$ on the x-axis is roughly the probit of the probability that a study with a small sample size (large standard error, SE) is published and $\gamma 1$ on the y-axis is roughly the regression coefficient of the change in the probit of the probability that a study with observed precision 1/SE is published. The line of steepest descent from the top right corner descending to the left indicates selection. Contours in this plot should be smooth.

Figure S98c. Effect plot. The effect estimates highlighted in the contour plot (b) are also shown in this plot including their 95% confidence intervals. Values on the x-axis are calculated using the largest standard error (SE) of all studies in the given meta-analysis

(the “smallest study”) and values for $\gamma 0$ and $\gamma 1$ from the contour plot. Selection increases on the x-axis from the left to the right (because the probability of publishing the study with the largest SE decreases).

Figure S98d. P-value plot. The plot shows the p-value for residual selection bias. A p-value of p = 0.1 is regarded as significant indicated by the horizontal dashed line. If the contour of estimated effects crosses the dashed line, the adjusted effect can be read off at this point of selection.

The contour plot showed smooth contours with ranges for γ_0 and γ_1 being appropriate and the line orthogonal to the contours was well chosen (Figure 98b). The Copas model (i.e., maximum likelihood) estimate and its confidence interval with no publication bias (left hand end, solid line) agreed with the random effects estimate shown by the gray horizontal line. As the probability of publishing the smallest studies decreases the effect confidence intervals generally were getting narrower. The mean effect and its confidence intervals vary smoothly to the right of the area and the confidence intervals do not cut the null value (Figure 98c). The Copas model p-value for residual selection bias was significant with p = 0.03 and the relationship between the p-value for residual selection bias and the probability of publishing the smallest study (largest SE) was completely smooth indicating no local problems with the estimation. The Copas selection model analysis does not overturn the conclusion of the original meta-analysis comparing acutely-ill anorexia nervosa cases with healthy controls as the adjusted estimate of -7.20 ng/mL (95% CI, -8.44, -5.96; p < 0.0001) with an estimated selection probability of 66% and 5 potentially unpublished studies is similar to the random effects model estimate with -7.90 ng/mL (95% CI, -9.72, -6.08) and has a comparable confidence interval.

8f) Body mass index post-treatment

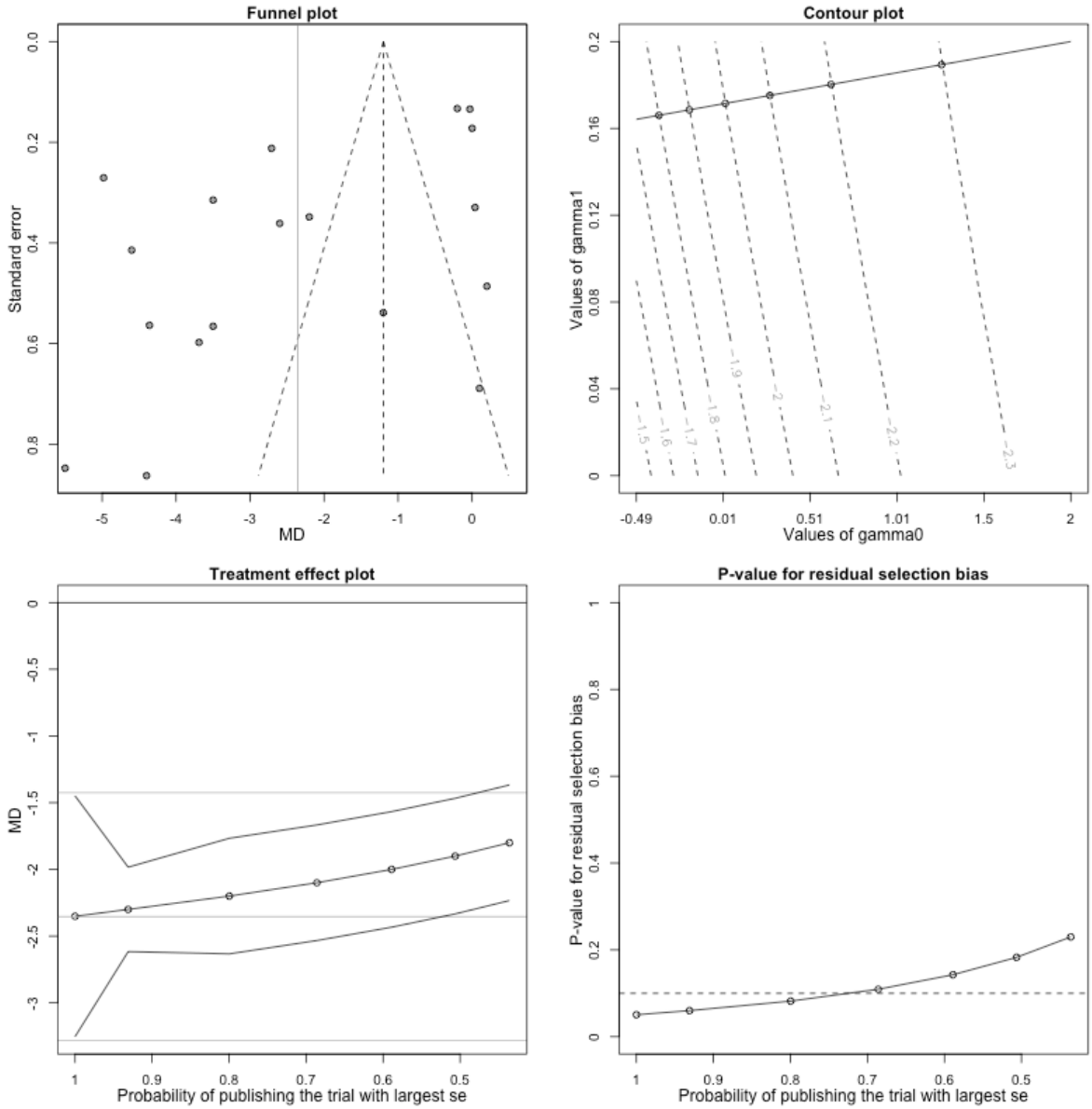

Figure S99. Copas model body mass index post-treatment

Figure S99a. Funnel plot for post-treatment body mass index. The vertical gray line corresponds the random effects model estimate and the diagonal dashed lines correspond to ± 2 standard errors (SEs). If there is no heterogeneity and no publication bias, 95% of all studies should lie within the funnel.

Figure S99b. Contour plot. The plot shows the estimated treatment effect for a range of pairs ($\gamma 0$ and $\gamma 1$). The Copas selection model has two sensitivity parameters: $\gamma 0$ on the x-axis is roughly the probit of the probability that a study with a small sample size (large standard error, SE) is published and $\gamma 1$ on the y-axis is roughly the regression coefficient of the change in the probit of the probability that a study with observed precision 1/SE is published. The line of steepest descent from the top right corner descending to the left indicates selection. Contours in this plot should be smooth.

Figure S99c. Effect plot. The effect estimates highlighted in the contour plot (b) are also shown in this plot including their 95% confidence intervals. Values on the x-axis are calculated using the largest standard error (SE) of all studies in the given meta-analysis

(the “smallest study”) and values for $\gamma 0$ and $\gamma 1$ from the contour plot. Selection increases on the x-axis from the left to the right (because the probability of publishing the study with the largest SE decreases).
Figure S99d. P-value plot. The plot shows the p-value for residual selection bias. A p-value of p = 0.1 is regarded as significant indicated by the horizontal dashed line. If the contour of estimated effects crosses the dashed line, the adjusted effect can be read off at this point of selection.

The contour plot showed smooth contours with ranges for γ_0 and γ_1 being appropriate and the line orthogonal to the contours was well chosen (Figure 99b). The Copas model (i.e., maximum likelihood) estimate and its confidence interval with no publication bias (left hand end, solid line) agreed with the random effects estimate shown by the gray horizontal line. As the probability of publishing the smallest studies decreases the effect confidence intervals generally were getting narrower. The mean effect and its confidence intervals vary smoothly to the right of the area and the confidence intervals do not cut the null value (Figure 99c). The Copas model p-value for residual selection bias was significant with p = 0.05 and the relationship between the p-value for residual selection bias and the probability of publishing the smallest study (largest SE) was completely smooth indicating no local problems with the estimation. The Copas selection model analysis does not overturn the conclusion of the original meta-analysis comparing post-treatment anorexia nervosa cases with healthy controls as the adjusted estimate of -2.10 kg/m^2 (95% CI, -2.53, -1.67; p < 0.0001) with an estimated selection probability of 64% and 11 potentially unpublished studies is similar to the random effects model estimate with -2.35 kg/m^2 (95% CI, -3.28, -1.42) and has a comparable confidence interval.

8g) Body fat percentage post-treatment

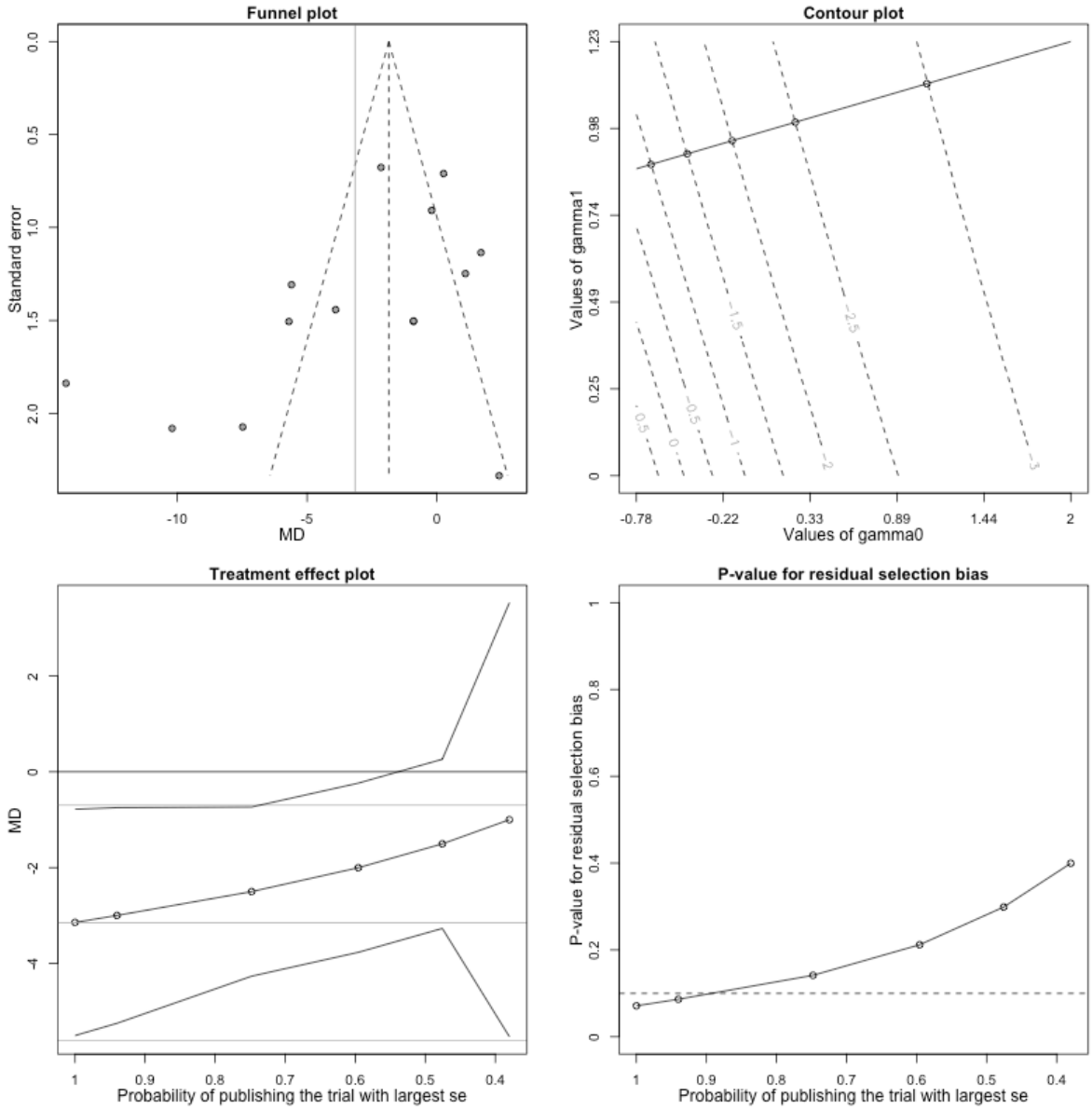

Figure S100. Copas model body fat percentage post-treatment

Figure S100a. Funnel plot for post-treatment body fat percentage. The vertical gray line corresponds the random effects model estimate and the diagonal dashed lines correspond to ± 2 standard errors (SEs). If there is no heterogeneity and no publication bias, 95% of all studies should lie within the funnel.

Figure S100b. Contour plot. The plot shows the estimated treatment effect for a range of pairs ($\gamma 0$ and $\gamma 1$). The Copas selection model has two sensitivity parameters: $\gamma 0$ on the x-axis is roughly the probit of the probability that a study with a small sample size (large standard error, SE) is published and $\gamma 1$ on the y-axis is roughly the regression coefficient of the change in the probit of the probability that a study with observed precision 1/SE is published. The line of steepest descent from the top right corner descending to the left indicates selection. Contours in this plot should be smooth.

Figure S100c. Effect plot. The effect estimates highlighted in the contour plot (b) are also shown in this plot including their 95% confidence intervals. Values on the x-axis are calculated using the largest standard error (SE) of all studies in the given meta-analysis

(the “smallest study”) and values for $\gamma 0$ and $\gamma 1$ from the contour plot. Selection increases on the x-axis from the left to the right (because the probability of publishing the study with the largest SE decreases).
Figure S100d. P-value plot. The plot shows the p-value for residual selection bias. A p-value of p = 0.1 is regarded as significant indicated by the horizontal dashed line. If the contour of estimated effects crosses the dashed line, the adjusted effect can be read off at this point of selection.

The contour plot showed smooth contours with ranges for γ_0 and γ_1 being appropriate and the line orthogonal to the contours was well chosen (Figure 100b). The Copas model (i.e., maximum likelihood) estimate and its confidence interval with no publication bias (left hand end, solid line) agreed with the random effects estimate shown by the gray horizontal line. As the probability of publishing the smallest studies decreases the effect confidence intervals generally were getting narrower. The mean effect and its confidence intervals vary smoothly to the right of the area and the confidence intervals do not cut the null value (Figure 100c). The Copas model p-value for residual selection bias was significant with p = 0.07 and the relationship between the p-value for residual selection bias and the probability of publishing the smallest study (largest SE) was completely smooth indicating no local problems with the estimation. The Copas selection model analysis does not overturn the conclusion of the original meta-analysis comparing post-treatment anorexia nervosa cases with healthy controls as the adjusted estimate of -2.5% (95% CI, -4.3, -0.7; p = 0.005) with an estimated selection probability of 74% and 3 potentially unpublished studies is similar to the random effects model estimate with -3.2% (95% CI, -5.6, -0.7) and has a comparable confidence interval.

8h) Trunk body fat percentage post-treatment

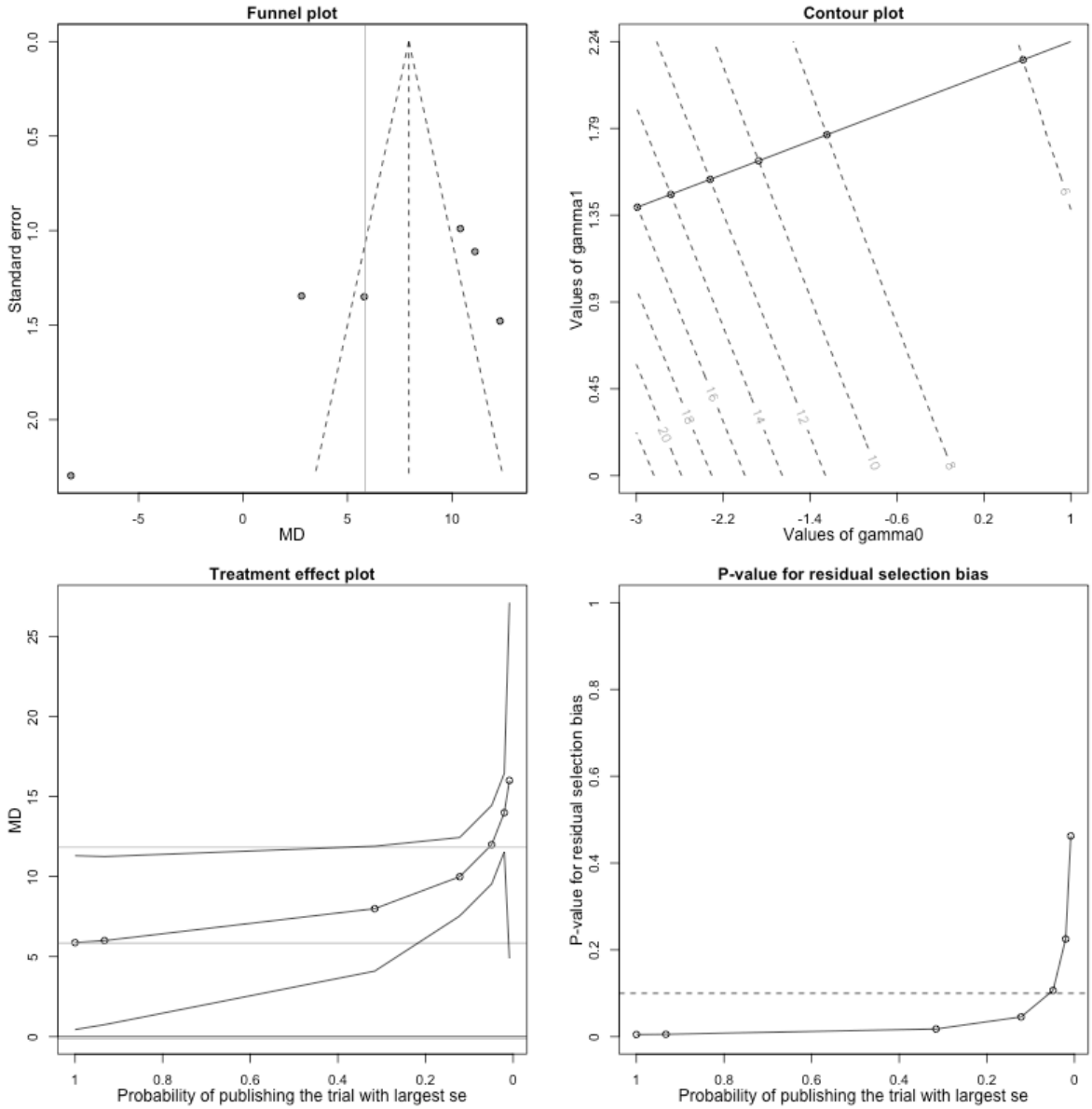

Figure S101. Copas model trunk body fat percentage post-treatment

Figure S101a. Funnel plot for post-treatment body fat percentage. The vertical gray line corresponds the random effects model estimate and the diagonal dashed lines correspond to ± 2 standard errors (SEs). If there is no heterogeneity and no publication bias, 95% of all studies should lie within the funnel.

Figure S101b. Contour plot. The plot shows the estimated treatment effect for a range of pairs ($\gamma 0$ and $\gamma 1$). The Copas selection model has two sensitivity parameters: $\gamma 0$ on the x-axis is roughly the probit of the probability that a study with a small sample size (large standard error, SE) is published and $\gamma 1$ on the y-axis is roughly the regression coefficient of the change in the probit of the probability that a study with observed precision 1/SE is published. The line of steepest descent from the top right corner descending to the left indicates selection. Contours in this plot should be smooth.

Figure S101c. Effect plot. The effect estimates highlighted in the contour plot (b) are also shown in this plot including their 95% confidence intervals. Values on the x-axis are calculated using the largest standard error (SE) of all studies in the given meta-analysis

(the “smallest study”) and values for $\gamma 0$ and $\gamma 1$ from the contour plot. Selection increases on the x-axis from the left to the right (because the probability of publishing the study with the largest SE decreases).
Figure S101d. P-value plot. The plot shows the p-value for residual selection bias. A p-value of p = 0.1 is regarded as significant indicated by the horizontal dashed line. If the contour of estimated effects crosses the dashed line, the adjusted effect can be read off at this point of selection.

The contour plot showed smooth contours with ranges for γ_0 and γ_1 being appropriate and the line orthogonal to the contours was well chosen (Figure 101b). The Copas model (i.e., maximum likelihood) estimate and its confidence interval with no publication bias (left hand end, solid line) agreed with the random effects estimate shown by the gray horizontal line. As the probability of publishing the smallest studies decreases the effect confidence intervals generally were getting narrower. The mean effect and its confidence intervals vary smoothly to the right of the area and the confidence intervals do not cut the null value (Figure 101c). The Copas model p-value for residual selection bias was significant with $p < 0.001$ and the relationship between the p-value for residual selection bias and the probability of publishing the smallest study (largest SE) was completely smooth indicating no local problems with the estimation. The Copas selection model analysis overturns the conclusion of the original meta-analysis comparing post-treatment anorexia nervosa cases with healthy controls as the adjusted estimate of 12.0% (95% CI, 9.54; 14.44; $p < 0.0001$) with an estimated selection probability of 5% and 52 potentially unpublished studies is different to the random effects model estimate with 5.8% (95% CI, -0.14, 11.83) and has a much narrower confidence interval. The adjusted point estimated was not included in the original confidence interval.

Appendix 3 Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa

Watson, H. J., Yilmaz, Z., Thornton, L. M., Hübel, C., Coleman, J. R. I., Gaspar, H. A., . . . Bulik, C. M. (2019). Nature Genetics.

3.1 Supplementary Note

3.1.1 Anorexia Nervosa Genetics Initiative

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3.2 Additional Methods

3.2.1 Samples and study design

Psychiatric Genomics Consortium (PGC) abbreviations for the 33 datasets meta-analyzed in this study are shown in **Supplementary Table 1**. **Supplementary Table 1** shows cohort case and control numbers, SNP numbers, and lambda at ascertainment [pre-quality control (QC)] and post-QC, **Supplementary Table 2** describes ascertainment including how cases were evaluated in the primary studies, and case and control sources and inclusion and exclusion criteria. **Supplementary Table 3** gives the genotyping platforms used. Details of the contributing studies and cohorts are provided below. The study is a secondary analysis of data collected from the studies described and did not involve direct recruitment and contact with participants or collection of identifiers linked to participants. The IRB of the University of North Carolina at Chapel Hill gave approval for this project (reference number 15-3307).

Eating Disorders Working Group of the Psychiatric Genomics Consortium (PGC-ED) Freeze 1

Full details of these data are given in the Freeze 1 paper of the PGC-ED (http://www.med.unc.edu/pgc) authored by Duncan et al.[1] To summarize, Duncan et al. datasets included the Children's Hospital of Philadelphia/Price Foundation Collaborative Group (CHOP/PFCG) case-control data from the anorexia nervosa GWAS of Wang et al.[6], case-only data from the Genetic Consortium for Anorexia Nervosa/Wellcome Trust Case Control Consortium-3 (GCAN/WTCCC-3; https://www.wtccc.org.uk) included in Boraska et al.[2], and since many of the controls used in Boraska et al. were not permitted to be re-used, control cohorts were sourced as described in Duncan et al.[1]. Control cohorts from a similar geographic location and genotyped on an Illumina platform were preferentially sought. Briefly, eethical approval for each site in GCAN/WTCCC3 was obtained from the local ethics committee. All participants provided written informed consent in accordance with the Declaration of Helsinki[1,2]. Ethical approval for each site in the PFCG was obtained separately from their own institution's human subjects committee. Informed consent was obtained from all study participants[3-5]. Controls for the PFCG cases were obtained from CHOP. The Research Ethics Board of CHOP approved the study, and written informed consent was obtained from all subjects or their parents[6]. All cases and controls in PGC-ED Freeze 1 were also included in the current analysis[1]. As per Freeze 1, the Italy-North cases from Boraska et al. were not included due to a lack of ancestrally-matched controls accessible for our study. Pre-QC datasets with < 100 cases were identified (Germany, Greece, Italy-South, Norway) and merged with other data to form larger datasets. The combinations were an excellent ancestral match according to principal components analysis (PCA). Italy-South and Greece were merged to form

the cohort *itgr*. Czech and Poland data were merged and formed the cohort *poco*, and Norway, Germany, and Sweden data were merged and formed the cohort *gns2* (see the section below called "Genetic Consortium for Anorexia Nervosa/Wellcome Trust Case Control Consortium-3" for information about Poland and Sweden data). These samples are included in *chop*, *fin1*, *fre1*, *itgr, gns2, net1, poco, spa1, ukd1, and usa1* (see the section below for other data in *poco* and *gns2*).

Genetic Consortium for Anorexia Nervosa/Wellcome Trust Case Control Consortium-3 (GCAN/WTCCC-3)

Additional GCAN/WTCCC-3 cohorts that were not part of Duncan et al. due to a lack of controls (Poland) or small $N < 100$ of cases (Sweden) were included in our analysis as we were able to identify ancestrally matched cases and/or controls. We sourced Poland controls from the BoMa/MooDS-PGC study (Bonn/Mannheim Bipolar study; Systematic Investigation of the Molecular Causes of Major Mood Disorders and Schizophrenia study)[7,8]. These controls were also used in the PGC bipolar disorder GWAS[9]. These controls were produced by the International Agency for Research on Cancer (IARC; https://www.iarc.fr) and the Centre National de Génotypage (CNG; https://www.cng.fr) GWAS Initiative for a study of upper aerodigestive tract cancers[10] and genotyped on the Illumina HH317k. They were drawn from a hospital-based case-control sample recruited by the Nofer Institute of Occupational Medicine in Lodz and a population-based case-control sample recruited by the Cancer-Center and Institute of Oncology in Warsaw. Controls were not screened for neuropsychiatric phenotypes. These combinations above proved an excellent ancestral match according to PCA. These samples are included in *poco* and *gns2*.

Anorexia Nervosa Genetics Initiative (ANGI)

ANGI is a multi-country effort to identify the genetic causes of anorexia nervosa and involves international research teams in the US, Sweden, Denmark, and Australia with assistance from New Zealand. Details on recruitment strategies, case definitions, and methods for ANGI have been reported previously and are outlined briefly below[11,12]. All ANGI controls were screened for eating disorder phenotypes and some for additional psychiatric phenotypes (https://www.med.unc.edu/psych/eatingdisorders/our-research/angi.

Australia and New Zealand (ANGI-ANZ). Cases from ANGI-ANZ were recruited the following way. Individuals who resided in Australia (age ≥ 13 years) or New Zealand (age ≥ 14 years) self-identified or were referred to the study. Those interested in study participation completed the consent process and online diagnostic questionnaire (ED100K-V1). Cases met anorexia nervosa criteria based on DSM-IV-TR. Once the questionnaire was completed, the participant provided a blood sample. In New Zealand, witnessed informed consent was obtained prior to sample collection. Genotyping was conducted at the Broad Institute on the Illumina

Global Screening Array. Controls were obtained from the QSkin Sun and Health Study (https://qskin.qimrberghofer.edu.au)[13]. Briefly, ~40,000 men and women aged 40-69 years were randomly sampled from Queensland, Australia. Those who indicated no eating disorders history from a checklist were included as controls. QSkin was established to study the etiology of cutaneous melanoma and other cancers of the skin; the cohort is followed up passively through linkage with health registers. QSkin participants provided Oragene saliva samples, and DNA was genotyped at Erasmus University Rotterdam in the Netherlands on the Illumina Global Screening Array. Ethical approval for the Australian component of the study was provided by the QIMR Berghofer Human Research Ethics Committee (QIMR-HREC approval P1339). Those interested in study participation completed the informed consent process via online submission prior to taking an online diagnostic questionnaire (ED100K-V1). Participants younger than 18 years then completed a paper questionnaire which required parent/guardian co-signature. Ethical approval for the New Zealand component was provided by the Health and Disability Ethics Committee of the New Zealand Ministry of Health. In New Zealand, witnessed informed consent was obtained prior to sample collection. Participants under 18 years required parent/guardian co-signature. Ethical approval for the QSkin study was provided by the Human Research Ethics Committee of the QIMR Berghofer Medical Research Institute (QIMR-HREC approval P1309). QSkin participants were given the option to provide written informed consent or to consent online in order to take part in the QSkin study. The samples described formed cohort *aunz*.

Denmark (ANGI-DK). National register and biobank. Cases and controls were identified primarily using the national register and biobank system. Genotypes came from Guthrie cards held by the Danish Neonatal Screening Biobank at Statens Serum Institute. Samples from this biobank are linked to the Danish register system via the unique Danish personal identification number. The individuals were born between 1981 and 2005 and had to be alive and a resident of Denmark on their first birthday and have a known mother. Cases had International Classification of Diseases (ICD-10) anorexia nervosa (F50.0)[14] diagnoses assigned by psychiatrists at inpatient and outpatient psychiatric services, and were identified using the Danish Psychiatric Central Research Register[15]. Controls were randomly selected from the same nationwide birth cohort. Cases and controls were specifically ascertained and genotyped as a part of ANGI, and additional control genotypes came from the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH; http://ipsych.au.dk)[16]. DNA from the dried blood spots was extracted, whole-genome amplified in triplicates, and genotyped in 23 batches based on birth year. The first wave (batch) contains the youngest participants (born in 2004) and wave 23 consists of the oldest participants (born in 1981). Wave 24, a supplementary batch, comprised all participants with an ICD-10 atypical anorexia nervosa lifetime diagnosis (F50.1, most commonly diagnosed

when all anorexia nervosa criteria except amenorrhea were met) up to and including 2013 and F50.0 cases diagnosed during 2013. Comparisons showed that F50.0 and F50.1 samples matched on register information tested, i.e., age of diagnosis, frequency of lifetime psychiatric diagnoses and intellectual disability, urbanicity, and maternal and paternal age at childbirth. Genotyping was performed on the Illumina PsychChip array at the Broad Institute of Harvard and MIT. GenCall[17] and Birdseed[18] were used to call variants with MAF > 0.01. Call sets were merged after pre-QC on individual call sets. Data processing and GWAS analyses were performed on secure servers at the GenomeDK high-performance computing cluster (http://genome.au.dk).

DNA preparation, genotyping, genotype calling, QC methods, and imputation were performed on the broader iPSYCH cohort waves, which also included psychiatric cases with non-anorexia nervosa diagnoses (schizophrenia, depression, bipolar disorder, autism spectrum disorder, and attention-deficit/hyperactivity disorder). The full iPSYCH cohort described contains ~86,000 individuals, including about 57,000 cases with at least one of the noted psychiatric disorders and around 30,000 controls. Each wave that was processed had ~3,500 participants.

Case-control data were filtered for the primary GWAS analysis such that cases required an anorexia nervosa or atypical anorexia nervosa lifetime diagnosis and controls required no lifetime anorexia nervosa or iPSYCH psychiatric diagnoses listed above. To address batch effects, a GWAS was conducted on waves separately, except waves 1 to 6 which were combined in a block due to smaller case sample sizes. Ancestry principal components (PCs) and PCs that captured batch effects and other possible sources of variation were included as covariates (**Supplementary Table 18**). ANGI-DK samples formed cohorts *w1* to *w24*.

Individuals in ANGI-DK did not provide written informed consent. The register data collection is pseudo-anonymi***z***ed (http://ipsych.au.dk/about-ipsych/data-processing-and-data-security-atipsych) and the re-identification key for linking the Danish civil registration number is stored separately from phenotype and genotype data. An exemption from consent is legally possible in Denmark if approved by The Danish Scientific Ethics Committee (Videnskabsetisk Komité). This exemption was given for all samples and was provided in 2012 to the iPSYCH study, with the most recent approval granted in 2018.

Denmark clinic samples**.** A Danish clinical cohort was obtained. Cases were defined as patients with at least one recorded hospital admission during which an ICD-10[14] diagnosis of F50.0 or F50.1 was given. Clinical cases consisted of women born 1947-1980 (age range: 35 to 68 years). Samples were genotyped at the Broad Institute on the Illumina Global Screening Array. Ethical approval with the protocol no. H-KF-01-024/01 was obtained from the competent Danish authority, De

Videnskabsetiske Komiteer for Region Hovedstaden (The Capital Region of Denmark's Committees on Health Research Ethics). All participants provided written informed consent prior to being included into the study. The samples described are included in cohort *sedk*.

Sweden (ANGI-SE). The primary recruitment strategy involved Riksät-National Quality Register for Eating Disorders Treatment[19], which includes eating disorder-specific information from individuals seeking eating disorder treatment in Sweden since 1999. Potential cases identified through Riksät were sent a letter asking them to complete a follow-up questionnaire, which included the ED100K-V1 questionnaire. In the second recruitment strategy, study nurses at the Stockholm Centre for Eating Disorders (http://stockholmatstorningar.se) (SCÄ) recruited cases for ANGI. When patients with anorexia nervosa came into this center, a research nurse discussed the study with them and reviewed the consent. When participants consented, a blood sample was taken, and the participant was directed to complete the online diagnostic questionnaire. The third strategy was community outreach, specifically using traditional media (i.e., TV, radio, and newspapers) and social media including the Swedish ANGI website (http://www.angi.se), directly linking to the questionnaire. The final recruitment strategy for cases and controls involved LifeGene (https://www.lifegene.se)[20], an ongoing study initiated in 2010 to evaluate how genes, environment, and lifestyle affect health. Individuals enrolled in LifeGene completed an eating disorder assessment similar to the online diagnostic questionnaire and provided a blood sample. An anorexia nervosa algorithm for LifeGene was harmonized with the ED100K-V1 questionnaire for case and control identification. All cases met anorexia nervosa criteria based on DSM-IV-TR[21], and controls screened negative for a history of eating disorders. Genotyping was performed at the Broad Institute on the Illumina Global Screening Array. The Swedish component of ANGI (Riksät, SCÄ, and Community) was approved by the Regional Ethical Review Board in Stockholm (dnr: 2013/112-31/2). Individuals who wished to participate were mailed consent forms along with the vials for blood samples. Signed consent forms were returned with the samples. The Regional Ethical Review Board of Stockholm provided initial ethical approval of LifeGene. All participants provided consent online[20]. The Swedish component of ANGI obtained approval, as stated above, for use of LifeGene samples and data as part of ANGI-SE. These samples described are included in cohort *sedk* (see the section above called "Denmark Clinic Samples" for other samples included in *sedk*.

United States (ANGI-US). Individuals who resided in the US (ages ≥ 12 years) self-identified or were referred to the study. Individuals completed a brief online screener to determine eligibility as a case or control for ANGI. Those deemed eligible completed the consent process and online diagnostic questionnaire (ED100K-V1). All cases met anorexia nervosa criteria based on DSM-IV-TR, and

controls screened negative for a history of eating disorders. Once the questionnaire was completed, the participant provided a blood sample. Approximately 1,000 controls were recruited from the community. Additional control samples were obtained from The Price Foundation Anorexia Nervosa Trios Study[5,22]. These additional controls reported no history of eating disorders, had no first degree relative with an eating disorder, and screened negative for other Axis I psychopathology. Genotyping was performed at the Broad Institute on the Illumina Global Screening Array. Ethical approval for the US component of ANGI was granted by the University of North Carolina at Chapel Hill's Institutional Review Board (IRB# 13-0081). Individuals who were interested in study participation (and deemed eligible by the brief screen in the US) contacted the study team and completed the consent process. Although some provided written consent, most participants provided consent over the phone after a complete review of the consent forms. These samples formed cohort *usa2*.

UK Biobank

The UK Biobank (http://www.ukbiobank.ac.uk/) is a large prospective study of ~500,000 residents of the United Kingdom aged from 40 to 69 years old[23]. UK Biobank aims to provide insights into the causes, prevention, and treatment of various illnesses. Recruitment occurred between 2006-2010. The present study uses data from the July 2017 release including the second wave of genetic data. Cases were identified by primary and secondary ICD-10[14] diagnosis from linked health care records and self-report diagnosis of anorexia nervosa by a clinical professional in the UK Biobank mental health questionnaire. Controls were screened for any psychiatric disorder (Chapter V: Mental and behavioral disorders). UK Biobank participants provided electronic signed consent at their baseline assessment visit. UK Biobank was approved by the NHS Health Research Authority North West-Haydock Research Ethics Committee (reference 16/NW/0274). The current study was completed as part of approved UK Biobank application 27456. The samples described formed cohort *ukbb*.

3.2.2 Merging of case and control data

When sourcing control data, we prioritized controls that were ancestrally matched and genotyped on a similar platform to cases. There are two instances whereby cases were matched with controls from another country [i.e., *aunz* New Zealand cases (n = 430) were merged with Australian cases (n = 2,261) and controls (n = 17,158), and *sedk* Denmark cases (n = 129) were merged with Sweden cases (n = 4,118) and controls (n = 4,035)]. Country is unlikely to be confounded with case-control status in these cohorts. Ancestral matching was undertaken by visual inspection of a principal components analysis PC1 v PC2 plot for the merged data, and the matches were excellent with cases and controls randomly interspersed. Further, the first five ancestry PCs and any PCs that significantly differed ($P < 0.05$)

between case and control cohort were included as covariates in GWAS to capture nuanced ancestry or batch effect differences.

3.2.3 Statistical power

Identified susceptibility variants in psychiatric genetics typically have an OR of ~1.1[24]. Our study was acceptably powered to detect susceptibility variants in this range (80% power to detect an OR of 1.09-1.19 with an additive model, 0.9% lifetime risk[25], $\alpha = 5 \times 10^{-8}$, MAF 0.05–0.5). Prior experience in other PGC disorders gives us reason to believe that when sample sizes reach an inflection point for power to detect multiple GWAS hits, the number of significant loci begins to increase linearly as samples were added after this inflection point. It is not surprising to see several borderline significant hits when first exceeding the inflection point, as has been observed in schizophrenia[26-28]. As more cases are added, it is probable that we will get more lead hits above this borderline range.

3.2.4 Quality control and covariates

For the GWAS analysis, the default QC parameters in Ricopili were used and are described as follows. Ricopili QC begins with a pre-filter SNP call rate of > 0.95, which is useful for cases and controls genotyped on different platforms. Next, QC involves sample filters, then SNP filters. Default sample filters are a call rate (cases/controls) ≥ 0.98, heterozygosity inbreeding coefficient ≤ 0.2 (cases/controls), and sex violations. Default SNP filters are a call rate ≥ 0.98, case-control missingness difference ≤ 0.02, no valid association *P* value (invariant), and violations of Hardy-Weinberg equilibrium (in controls $P > 10^{-6}$, in cases $P > 10^{-10}$). Some cohorts required the application of more stringent thresholds to reduce bias (**Supplementary Table 18**). Ancestry outliers were removed based on plotting the first two principal components (PCs) in a principal components analysis (PCA) containing each cohort and five reference cohorts (1000 Genomes Phase 3 EUR, AFR, EAS, SAS, AMR)[29] to retain European samples. Samples showing familial structure and/or cryptic relatedness, or duplicates were removed ($\hat{\pi} > 0.2$) during PCA. For the Danish waves, we conducted additional relatedness testing across all the waves combined, and then removed one individual from each related pair ($\hat{\pi} > 0.2$). PCs significantly associated with the phenotype were identified for inclusion as covariates. For the *aunz* cohort, QC and PCA was done externally. For QC, see **Supplementary Table 18**. PCA (20 principal components) were computed using smartpca (EigenSoft 6.0.1) on the cleaned data from all individuals used in the current paper in conjunction with the genotypes of ~50,000 additional individuals available at QIMR Berghofer, and the population reference data from the Genome-EUTWIN populations (https://ega-archive.org/datasets/EGAD00000000043) and HapMap Phase 3 populations[30]. Analyses were run using a filtered set of genotypes available across all genotyping projects (*N* SNPs ~40,000). Individuals beyond six standard deviations (*SD*s) of the European PC1 and PC2 centroid were excluded from analysis. The data were then put through Ricopili PCA module; the first five

ancestry components and PCs significantly associated with the phenotype were always included as covariates (**Supplementary Table 18**). To the extent that national laws and regulations permitted, we examined sample overlap across cohorts by performing LD score bivariate regressions and estimating genetic covariance intercepts to assess sample overlap[31,32] (**Supplementary Table 19**).

Some of the cohorts required additional QC beyond the default process and parameters used in PGCs GWAS pipeline, Ricopili. **Supplementary Table 18** shows the additional QC steps applied, if any, and the PCs used as covariates, by cohort. The first five PCs were automatically included to adjust for ancestry effects. Tests were done on post-QC data to investigate whether any of the PCs differ significantly between cases and controls, and if so, PCs nominally associated with the phenotype ($P < 0.05$) were also included in the GWAS as covariates.

3.2.5 Anorexia nervosa subtype phenotypes

We defined subtypes based on the presence or absence of binge eating. The rationale for this choice was that the current DSM-5[33] subtyping (i.e., restricting versus binge/purge) is a clinical, rather than a biological distinction. "Purging" behavior is a heterogeneous category and includes several behaviors either alone or in combination (e.g., self-induced vomiting, laxative abuse, diuretic abuse, other inappropriate compensatory behaviors), and our sample size is insufficiently powered—and phenotyping in several samples inadequately detailed—to identify individuals with various purging behavior constellations. In contrast, binge eating is more uniformly defined, represents a clear departure from restrictive eating behavior, and lies on the appetite continuum. Although the twin-based genetic correlation between binge eating and self-induced vomiting is high ($r_g = 0.74$)[34], less is known about other purging methods. Larger samples sizes will enable additional group distinctions and allow us to comment on the biological appropriateness of the current DSM-5 subtypes.

We defined anorexia nervosa with and without binge eating using available phenotypic data. We were able to use *chop*, *aunz*, and *usa2* datasets for this analysis. For *aunz* (ANGI-ANZ) and *usa2* (ANGI-US), anorexia nervosa with binge eating was defined as reporting ever 1) "having eating binges when you ate what most people would regard as an unusually large amount of food in a short period of time" and 2) "having a sense of loss of control during those eating binges". The absence of binge eating was determined by a "no" answer to either item. For *chop* (CHOP/PFCG), the presence of binge eating was defined as reporting a history of binge eating by structured or semi-structured interview. The no binge eating group had to report no lifetime history of bulimia nervosa and no history of binge eating. Purging was not used in these definitions and binge eating did not need to occur within episodes of anorexia nervosa. The percentage of available subtype data

within these cohorts was 95% overall. Future analyses with larger samples sizes will increase confidence in results from this analysis.

3.2.6 GWAS of related traits in UK Biobank

Seven UK Biobank GWAS were performed to facilitate genetic correlation investigations. The phenotypes were BMI (Hübel, Gaspar, Coleman, Hanscombe, Purves…Breen, unpublished report), body fat percentage[35], fat mass (Hübel, Gaspar, Coleman, Hanscombe, Purves…Breen, unpublished report), fat-free mass[35], physical activity[35], anxiety[36], and neuroticism[35].

3.2.7 Genotyping, imputation and QC

Briefly, blood samples were genotyped on two arrays, which share nearly all of their content: the UK BiLEVE array (N = 49,949) or the UK Biobank Axiom array (N = 438,414). Genotyping was conducted by Affymetrix across 33 different batches of approximately 4,700 samples each. UK Biobank provides extensive information on sample processing on its website (biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155583). UK Biobank performed stringent QC on the genotyping data at the Wellcome Trust Centre for Human Genetics (WTCHG). For further details, see: biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155580. Prior to imputation, all variant sites with a call rate below 90% were filtered out. Imputation was carried out by UK Biobank using a merged UK10K-1000 Genomes Phase 3 reference panel and the Haplotype Reference Consortium (HRC) panel[37] (for further information, please see [38]). UK Biobank preferentially retained SNPs imputed to HRC for SNPs present in both imputation panels. Imputation was conducted using the IMPUTE4 program[38].

We excluded non-European participants identified by k-means clustering (k = 4) on the first two PCs derived from the genotype data, and related individuals (KING relatedness metric > 0.088, equivalent to an identical-by-descent coefficient of 0.25). SNPs were excluded if they had a MAF < 1%, if no call was made in > 2% of samples following imputation, if they were imputed with low confidence (INFO < 0.8), deviated substantially from Hardy-Weinberg equilibrium (HWE test, $P < 10^{-7}$), if they were not genotyped and were not part of the HRC panel. Additional QC and other information about these GWAS is given in **Supplementary Table 20**.

3.2.8 GWAS of BMI, body fat percentage, fat mass, and fat free mass

The GWASs on BMI, body fat percentage, fat mass, and fat free mass were a cross-sectional analysis of 155,961 healthy European participants from the UK Biobank. To identify genetic variation uniquely associated with body composition not confounded by illnesses and their downstream effects or metabolism-altering medication, we applied stringent exclusion criteria (e.g., psychiatric,

gastrointestinal and endocrine illnesses, hormonal and antidiabetic medication). Body composition was assessed using Tanita BC-418 MA scale (Tanita Corporation, Arlington Height, IL). We included 7,794,483 genotyped and imputed SNPs and insertion-deletion variants with a MAF ≥ 1%. We covaried for assessment center, genotyping batch, smoking status, alcohol consumption, menopause, age, and socioeconomic status (measured by the Townsend Deprivation Index)[39]. We accounted for underlying population stratification by including the first six ancestry PCs, calculated on the European subsample GWAS cohorts. We used BGENIE v1.2 (https://jmarchini.org/bgenie) for sex-specific analyses and meta-analyzed these sex-specific GWAS using METAL[40] (http://csg.sph.umich.edu/abecasis/metal).

3.2.9 GWAS of physical activity

We calculated sex-specific GWAS of physical activity with imputed genotype data in 29,496 male and 36,758 female (*N* = 66,254) individuals in the UK Biobank, including age (at recruitment), genotyping array, and genetic PCs 1–20 as covariates. Physical activity in the UK Biobank was measured continuously over a period of seven days with a wrist-worn accelerometer. General physical activity quality control of raw data is described in detail elsewhere[41]. They used a wear-time adjusted 7-day average measure of activity, including only individuals meeting UK Biobank QC criterion: good wear-time, good calibration, calibration on own data, and no problem indicators. Analyses were performed on the intersection of this UK Biobank subset with those passing general genotyping QC: in European ancestry subset; used in the calculation of ancestry PCs; without excess relatives in the UK Biobank sample; no putative sex chromosome aneuploidy; and were not outliers for heterozygosity and genotype missingness. General genotyping considerations, raw data QC, and imputation procedure in the UK Biobank are described in detail elsewhere[38]. 20 PCs provided by the UK Biobank were used.

3.2.10 GWAS of anxiety

We conducted sex-specific GWAS of anxiety disorders with imputed genotype data on 25,443 cases and 58,113 controls[36]. Cases met criteria for probable lifetime anxiety disorder diagnosis if they either self-reported a professional diagnosis of any of the five core anxiety disorders (generalized anxiety disorder, panic disorder, specific phobia, agoraphobia, or social anxiety disorder) or met criteria for probable lifetime generalized anxiety disorder according to the Composite International Diagnostic Interview question set[42,43]. Cases did not report a diagnosis of schizophrenia, psychosis, attention-deficit/hyperactivity disorder (ADHD), autism, any eating disorder, or bipolar disorder. Controls were screened for any evidence of psychiatric or substance use disorders. Participants were limited to individuals of European ancestry, who were not excessively related, had no putative sex chromosome aneuploidy, and were not outliers for heterozygosity and genotype missingness. Stratified linear regressions were performed on ~7

million SNPs of high imputation quality (INFO > 0.9) with a minimum MAF ≥ 0.01 in BGENIE v1.2 controlling for six ancestry PCs calculated on the European subsample of UK Biobank, assessment center, genotyping batch, and age.

3.2.11 GWAS of neuroticism

We performed sex-specific GWAS on neuroticism using the genotype data supplied by UK Biobank in males (*N* = 142,875) and in females (*N* =144,660; total *N* = 287,535), following QC as described above and using PCs calculated on the European subsample of UK Biobank. The neuroticism phenotype was calculated as the sum score of neuroticism questions at the baseline assessment[44], corrected for age and sex-specific means and *SD*s from the UK population[45]. In a second analysis, individuals were excluded if they reported any psychiatric illness resulting in 83,413 males and 73,946 females (total *N* = 157,355). Sex-stratified linear regressions were performed in PLINK using eight ancestry PCs and genotyping batch (as a factor) as covariates and later meta-analyzed using METAL[40].

3.2.12 Gene expression

We first investigated whether anorexia nervosa heritability was enriched in tissue/cell type specifically expressed genes using publicly available gene expression data: GTEx[46] (RNA-seq of macroscopic samples from multiple human tissues) and Cahoy[47] (mouse neural cell-types transcriptome database). Stratified LDSC estimated common variant heritability enrichment in the top 10% of specifically expressed genes in each tissue or cell type, taking into account confounders such as gene size, LD, and functionally enriched genomic regions (e.g., conserved regions across mammals[48]. We followed a published method LDSC-SEG (LDSC applied to specifically expressed genes)[49]. From the datasets, the method has derived a genome annotation corresponding to each tissue or cell type of interest, which contains the top 10% specifically expressed genes of the tissue or cell type together with 100 Kb windows on each side of the transcribed region of each genes. We obtained the derived genome annotations from the LDSC-SEG GitHub repository (https://github.com/bulik/ldsc).

Second, we created a new annotation by performing differential expression analyses among 9,970 single cells, previously clustered into 24 different cell types[50], from five different mouse brain regions. Briefly, we used the scran R package[51] using the 50% of the genes with mean expression higher than the median to compute normalization factor for each single cell. The normalization factors were computed after clustering cells using the scran package quickCluster function to account for cell type heterogeneity. We then performed 24 differential expression analysis using R package BPSC[52] testing each cell type against the 23 other cell types using the computed normalization factors as a covariate. We then selected the top 10% most upregulated genes for each cell type and used the

coordinates of these genes extended by 100 Kb on each side as an extra annotation in LDSC.

We used the "munge_sumstats.py" script built in the LDSC software[31,32] to reformat the ANGI GWAS results. We then applied stratified LDSC regression to estimate heritability enrichment of the annotations[49] (tissue or cell type) conditional on 53 other annotations from the "baseline model" (e.g., conserved regions[48]). We used regression weights computed from phase 3 of the 1000 Genome Project[29] with HLA regions removed (https://data.broadinstitute.org/alkesgroup/LDSCORE/1000G_Phase3_weights_hm3_no_MHC.tgz).

We primarily report the regression coefficient of each annotation (corresponding to gene expression of each tissue or cell type) and an associated *P* value. A positive regression coefficient suggests that the annotation contributes to the heritability of anorexia nervosa while accounting for the contributions of other annotations[49,53]. The *P* value tests whether the regression coefficient was significantly positive (one-tailed), i.e., whether the contribution of the annotation is statistically significant. LDSC analyses are reported in **Supplementary Figs. 12-15**.

We also used MAGMA[54] (v1.06) (https://ctg.cncr.nl/software/magma), as done previously[50], to identify tissues/cell types underlying anorexia nervosa. GTEx data (V6p, median expression across individual per tissue) was downloaded from the GTEx website (https://gtexportal.org/home). Genes not expressed in any tissues (median = 0 for all tissues) were excluded. Gene expression from the different brain cell types was obtained as previously described. Briefly, we performed single cell RNA-seq from 9,970 single cells from five brain regions (neocortex, hippocampus, hypothalamus, striatum, midbrain, plus samples enriched for oligodendrocytes, dopaminergic neurons, and cortical parvalbuminergic interneurons), which allowed us to identify 24 cell types at level 1 (broad clustering) (pyramidal neurons, oligodendrocytes, etc…) and 149 cell types at level 2 (fine grained clustering) (pyramidal neurons from layer 6, layer 4, etc…).

For each gene expression dataset, we computed an index of specificity for each gene in each tissue/cell type by dividing the expression of a gene in a given tissue/cell type by the total expression of the gene in all tissues/cell types (range of specificity: 0-1). For each tissue/cell type, we then binned the specificity measure into 41 bins (0 representing a gene not expressed in the tissue/cell type, 1 gene in the bottom 2.5% quantile of specificity, …, 40 genes that are in the 97.5% to 100% most specific genes in the tissue/cell type). We then used MAGMA to test for a positive correlation between binned tissue specificity and gene-level genetic association with anorexia nervosa for each tissue/cell type. The gene-level genetic association was computed with MAGMA (v1.06) using a window surrounding the

gene by 35 kb upstream to 10 kb downstream of the gene. The gene-level association is computed by summing the association *P* value of SNPs located in the gene windows taking into account the LD structure of the region. MAGMA takes into account confounders such as gene length, LD, and gene-gene correlation. MAGMA analyses are reported in **Supplementary Figs 9-11.**

3.2.13 Predicted tissue-specific gene expression

We predicted differential gene expression using S-PrediXcan v1.0[55] and genomic and transcriptomic reference data from the brain regions assayed in the GTEx project v7[46] and Depression Genes and Networks (DGN) whole-blood cohort[56]. A total 258,158 gene-tissue pairs were tested (**Supplementary Table 13**). Significant genes were compared to genes in the gene-wise analysis performed with MAGMA.

3.2.14 A general note on multiple testing correction

Carrying out multiple testing runs the risk of inflating Type I error and increases the probability of false positive results. To manage this risk, we took the general approach of setting a conservative *a priori P* Bonferroni correction threshold. We did this generally on a within-analysis basis, since different analyses tested different underlying hypotheses, rather than paper-wide. Readers can identify the Bonferroni threshold used for a given analysis in Table and Figure notes.

3.3 Additional Results

3.3.1 Primary GWAS meta-analysis

Pre- and post-QC lambda, number of single-nucleotide polymorphisms (SNPs), and *N*s in each of the final 33 datasets analyzed within the primary GWAS can be found in **Supplementary Table 1**. The meta-analysis LD intercept was 1.02 (s.e. = 0.01). The meta-analysis quantile-quantile (Q-Q) plot is shown in **Supplementary Fig. 1**. The LD score regression intercepts for each cohort after QC ranged from 0.98 (s.e. = 0.01) to 1.03 (s.e. = 0.01) (**Supplementary Table 1**). The genetic covariance intercepts in LD score bivariate regression analyses were close to 0 and indicated no evidence of sample overlap among the cohorts (**Supplementary Table 19**). Eight genome-wide significant loci were identified. Follow-up analyses included using genome-wide complex trait analysis (GCTA-COJO)[57] to conduct stepwise regression on markers with *P* values < 10^{-8}. GCTA-COJO identified eight independent signals taking into account the LD correlations between SNPs and running a conditional and joint analysis[58]. All eight identified markers were equivalent to the SNPs resulting from distance- and LD-based clumping shown in **Table 1** (for conditional analyses please see **Supplementary Table 5**).

3.3.2 Genomic inflation and residual confounding

Here we provide detailed information to illustrate that confounding due to population stratification or other reasons was minimal in our primary GWAS. Two relevant parameters were estimated using linkage-disequilibrium (LD) score regression[29]. Firstly, we estimated an LD intercept of 1.02 (s.e. = 0.01) for the meta-analysis and between 0.98-1.03 for individual datasets (**Supplementary Table 1**). The LD score intercept is significantly greater than one, but is in line with the expected small levels of inflation caused by sample size and heritability described in Loh et al.[59]. A second measure, the attenuation ratio [(LDSC intercept – 1) / (mean χ^2 – 1)] for the meta-analysis was 0.07 (s.e. = 0.04) (**Supplementary Fig. 1**), also suggesting a lack of confounding. Together these suggest that deviation from the null was due to polygenic signal and not population structure or bias.

The overall inflation of summary statistics genomewide or λ_{GC} for individual datasets post-QC ranged between 1.00-1.06 (**Supplementary Table 1**) and for the meta-analysis was 1.22 **(Supplementary Fig. 1**). Inflation of tests statistics is known to be due to a combination of polygenicity, uncorrected population stratification, and confounding. The larger λ_{GC} value observed for our GWAS meta-analysis is indeed expected at this sample size, trait polygenicity, and heritability[59]. The LD score regression method for GWAS of highly polygenic phenotypes such as anorexia nervosa and large sample sizes separates the polygenetic component (the slope) from population stratification and other systematic biases (estimated by the intercept and attenuation ratio) [29].

Correcting for λ_{GC} in large GWAS samples of polygenic phenotypes can cause loss of signal and power, as evidenced by the LD intercept of the GWAS summary statistics

from the Genetic Investigation of Anthropometric Traits (GIANT) Consortium 2015 body mass index (BMI) paper (0.65)[60,61]. Correction for λ_{GC} at the individual study level has also been shown to bias heritability estimates downward[29].

3.3.3 Previous hit

The chr12 locus identified in Duncan et al.[1] did not reach genome-wide significance. The OR for the index variant at this locus (rs4622308) was in the same direction in the present meta-analysis compared with Duncan et al. (present: A1 = C, A2 = T, OR = 1.06, s.e. = 0.01, $P = 7.02 \times 10^{-5}$; Duncan et al.: A1 = C, A2 = T, OR = 1.20, s.e. = 0.03, $P = 4.25 \times 10^{-9}$) and in 22 of the 33 cohorts ($z = 2.00$, $P = 0.05$, 2-tailed). To further assess this locus, a random-effects meta-analysis was conducted. Similar to the fixed-effect meta-analysis, the random-effects meta-analysis indicated that the effect of this locus was not genome-wide significant (OR = 1.06, s.e. = 0.05, $P = 0.02$) and showed evidence of heterogeneity, $I^2 = 53.7$ (**Supplementary Fig. 4**). There are many possible reasons why the result was not replicated, including winner's curse[62], moderator variables given the heterogeneity observed (such as environmental risks), between-study heterogeneity in ascertainment, and differences in LD structure across cohorts in addition to true non-replication.

3.3.4 Chromosome X

The separate analysis of chrX included $n = 14{,}915$ cases and $n = 27{,}854$ controls. There were no genome-wide ($P < 5 \times 10^{-8}$) or suggestive ($P < 1 \times 10^{-5}$) significant loci.

3.3.5 Female-only secondary GWAS

A supplementary analysis conducted on female cases and controls only—to determine the similarity of results to the main GWAS analysis which included females and males—had 14,896 cases and 27,865 controls. The female-only GWAS revealed one genome-wide significant locus ($P < 5 \times 10^{-8}$) on chr3 (rs9812977; 48.2-49 Mb; $P = 1.31 \times 10^{-9}$; OR = 1.08; 95% CI: 1.03-1.14), which was the top locus in the main GWAS analysis.

3.3.6 eQTL and Hi-C interactions

For locus 1 (multigenic, chr3:47.5-51.3 Mb, **Supplementary Fig. 5a**), our data implicate 100 brain-expressed genes. Locus 1 is gene-dense with a large number of brain eQTLs and regulatory chromatin interactions. Notably, 16 genes with regulatory chromatin interactions mapping to the locus lie outside the LD-defined locus. Locus 3 (multigenic, chr2:53.8-54.3 Mb, **Supplementary Fig. 5c**) is less complex that locus 1. Nonetheless, we implicate 12 genes, six within and 6 outside the LD-defined locus.

For all four single-gene loci, eQTL and/or chromatin interaction connections implicated the gene intersecting the locus. For locus 2 (chr11:114.9-115.4 Mb, **Supplementary Fig. 5b**), both eQTL and regulatory chromatin interaction data confirmed the connection to the locus-intersecting gene *CADM1*. Genetic variants near to *CADM1* (cell adhesion molecule 1) have been implicated by GWAS for body mass and age at menarche. CADM1 protein levels appear to be elevated in the hypothalamus of BMI risk variant carriers. Obese mice have been reported to show elevated *CADM1* expression and *CADM1* knockout mice show reduced body weight[63]. For locus 4 (chr10:131.2-131.4 Mb, **Supplementary Fig. 5d**), eQTL data connected to the locus-intersecting gene *MGMT*. *MGMT* (O-6-methylguanine-DNA methyltransferase) encodes an epigenetic regulator important in multiple cancers, including glioblastoma. For locus 5 (chr3:70.6-71.0 Mb, **Supplementary Fig. 5e**), regulatory chromatin interaction data confirmed the connection to the locus-intersecting gene *FOXP1* (forkhead box P1), which encodes a transcription factor in the forkhead box family. Brain-specific deletion of *FOXP1* results in defects in striatal development and changes in the hippocampus[64]. Interestingly, *FOXP1* knockout mice exhibit a significant reduction in body weight as compared to littermate controls. For locus 5, eQTL data also suggested a functional connection to the more distal *GPR27*, which encodes an orphan G-protein coupled receptor, and is highly expressed in the brain[65]. It has recently been associated with insulin secretion[66]. Finally, for locus 6 (chr1:96.6-97.2 Mb, **Supplementary Fig. 5f**), both eQTL and regulatory chromatin interaction data confirmed the connection to the locus-intersecting gene *PTBP2*. The protein encoded by this gene binds to intronic polypyrimidine clusters in pre-mRNA molecules and is implicated in controlling the assembly of other splicing-regulatory proteins.

One intergenic locus (locus 8, chr5:93.9-95.0 Mb, **Supplementary Fig. 5h**) had eQTL connections to *PROS1* and *ARL13B*. *PROS1* encodes an anticoagulation factor that plays a role in blood-brain-barrier integrity[67]. *ARL13B* encodes a member of the ADP-ribosylation factor-like (ARL) small Ras GTPase family. ARL13B protein is expressed in the cilia of all organs; mutations are associated with Joubert syndrome 8, which like other ciliopathies has been associated with obesity[68,69]. Mutations are also associated with intellectual disability (University of Chicago's Intellectual Disability Exome Panel). Thomas et al.[69] found *ARL13B* expression throughout the developing human brain. Additionally, they identified *ARL13B* expression in primary cilia of hypothalamic neurons of newborn mice. Furthermore, Higginbotham et al.[70] found that mutant ARL13B disrupts the development and migration of interneurons.

For locus 7 (intergenic, chr5:24.9-25.3 Mb, **Supplementary Fig. 5g**), there were no supporting eQTL or regulatory chromatin interactions.

3.3.7 Multi-trait conditional and joint analysis (mt-COJO)

Seven of the eight genome-wide significant loci showed only slight changes in their effect sizes (i.e., betas) after conditioning on education years[71], type 2 diabetes[72], high-density lipoprotein (HDL) cholesterol[73], BMI (Hübel, Gaspar, Coleman, Hanscombe, Purves…Breen, unpublished report; see **Additional Methods**), schizophrenia[28], or neuroticism[35]. The results suggest that the loci are independent of the traits on which they were conditioned and that the traits may not share genetic association at these loci. The association of locus 2 on chr11 tagged by rs6589488 with anorexia nervosa may not be independent of genetic associations with type 2 diabetes as the beta was diminished after conditioning. This suggests, at locus 2, that the association with anorexia nervosa may not be independent of genetic underpinnings of glycemic alterations seen in type 2 diabetes.

3.3.8 Clinical investigations

3.3.9 Anorexia nervosa subtype

One potential source of genetic heterogeneity lies in differing clinical presentations of anorexia nervosa (i.e., with or without the presence of binge eating). This was not supported in preliminary analyses. The SNP-based genetic correlation (SNP-r_g) between the anorexia nervosa subtypes was 0.74 (s.e. = 0.16; $P = 1.74 \times 10^{-6}$). To test for heterogeneity in the genetic variation associated with these two subtypes, we tested whether their SNP-r_g was significantly different from unity. We used a block jackknife approach using the LD score regression software (LDSC) v1.0[29]. The genetic correlation between anorexia nervosa with and without binge eating was not significantly different from 1 ($P = 0.08$). There were no significant differences in the mean polygenic risk score (PRS) between subtypes in the three cohorts for which anorexia nervosa subtype data were available (**Supplementary Fig. 6**). We also calculated SNP-r_g by anorexia nervosa subtype (**Supplementary Table 9)** and found no significant differences in SNP-r_g with external traits, although small sample sizes limit interpretation. In summary, our preliminary subtype analyses do not indicate significant differences in the genetic architectures of anorexia nervosa with and without binge eating; however, larger sample sizes are necessary for confirmation.

3.3.10 Males with anorexia nervosa

The number of males identified on the basis of genotype sex in the meta-analysis was 447 cases and 20,347 controls. Anorexia nervosa PRS scores derived using the female-only GWAS were associated with a higher risk of anorexia nervosa in males. Those at the highest decile had 4.13 (95% CI: 2.58, 6.62) times the odds of lifetime anorexia nervosa compared with those at the lowest decile. Anorexia nervosa PRS accounted for ~1.8% of the total variance in anorexia nervosa in males for the discovery cohort *P* threshold (pT) = 0.5, comparable to ~1.7% at *P* threshold (pT) = 0.5 in the cohort as whole. Taken together, these preliminary results do not provide evidence for a major sex-specific difference in the common genetic

architecture of anorexia nervosa, although our conclusions are limited due to the small sample size.

3.3.11 Within-trait prediction: polygenic risk scoring

We observed that across cohorts, anorexia nervosa cases were more likely to be in the PRS higher deciles than controls based on their anorexia nervosa genetic load **(Supplementary Fig. 16)**. Visual inspection of the decile plots showed that the score distributions across deciles were relatively uniform across target datasets; thus, there was no indication of any extreme outlying datasets. PRS applied to the largest target dataset, *sedk*, showed that those at the highest decile had 2.59 times higher odds (95% CI: 2.12-3.18) of lifetime anorexia nervosa compared with those at the lowest decile. The results also provide evidence of the replicability of the main GWAS results (**Supplementary Fig. 16**).

3.3.12 Gene-wise analysis

Results of MAGMA gene-wise associations are reported in **Supplementary Table 11**. Seventy-nine genes were Bonferroni-significant (threshold = 2.62×10^{-6}), and 506 had a Benjamini and Hochberg[74] FDR q value < 0.05. None of the 79 Bonferroni-significant genes are part of the MHC, but 57 genes are located in a gene-rich locus on chr3. The top genes on chr3 were *NCKIPSD*, *CELSR3,* and *IP6K2*. Through the MAGMA analysis we identified 16 additional genes which were not annotated via clumping. These 16 genes are located in loci on chr 1, 2, 3, 7, 10, 11, 12, 17, and 22. Some of these Bonferroni-significant genes have been indicated to be involved in glycemic and metabolic disease phenotypes (*CTNNB1*[75]; *EXOC4*[76]; *FAM19A2*[77]; *VAMP2*[78]).

3.3.13 Pathway analysis

The Bonferroni-significant pathway (**Supplementary Table 12**) GO:positive_regulation_of_embryonic_development (Gene Ontology, 32 genes, 6.31×10^{-6}) has two Bonferroni-significant genes: *DAG1* and *CTNNB1*. *CTNNB1* encodes beta-catenin, an essential component of the canonical Wnt signaling pathway. Beta-catenin can regulate neuronal progenitor proliferation and affect cortical size[79]. *CTNNB1* expression has been associated with adipogenesis, glucose metabolism, and obesity[75]. Metabolic diseases including obesity and type 2 diabetes are influenced by genetic and functional variations in the Wnt signalling pathway[75]. *DAG1* encodes dystroglycan, an essential member of the dystrophin-glycoprotein complex that has been mainly studied in the context of muscular dystrophies. Dystroglycan and other members of the dystrophin-glycoprotein complex are also found in neurons and glia and their disruption has been linked to intellectual disability and altered brain development[80]. Specific ablation of dystroglycan in neurons or glia results in distinct phenotypes[81]. Dystroglycan is expressed in pyramidal cells of the cortex and hippocampus, where it appears to

be essential for the establishment and maintenance of CCK-positive basket cell terminals[82].

3.3.14 Tissue and cell type analyses

We first used partitioned heritability analyses in LDSC using annotation of elements in the genome with specific functions. Considering general annotations, enrichment in conserved regions was the main finding (enrichment (s.e.) = 24.97 (3.29), $P = 3.32 \times 10^{-11}$, **Supplementary Fig. 7**). Partitioned heritability analysis was then used to test for cell type-specific enrichment in the GWAS of anorexia nervosa among 10 cell type groups: adrenal and pancreas; cardiovascular; CNS; connective and bone; gastrointestinal; immune and hematopoietic; kidney; liver; skeletal muscle; and other tissue (which includes adipose tissue). The CNS cell type group showed a 2.8-fold significant enrichment (**Supplementary Fig. 8**).

We next investigated whether there were tissue or cell type associations with anorexia nervosa using gene expression data to annotate gene sets characteristic of specific cells or tissues (for details see[50]). Gene expression datasets used were: GTEx (RNA-seq of samples from multiple human tissues); gene expression from neurons; astrocytes and oligodendrocytes from developing and mature mouse forebrain[47]; and gene expression from 149 mouse brain cell types (KI level 1: 24 broad categories, KI level 2: 149 cell types underlying the 24 broad categories)[50].

Using MAGMA[54], the majority of brain tissues in GTEx were significantly associated with anorexia nervosa (**Supplementary Fig. 9**), the strongest hits being brain cerebellum and brain cerebellar hemispheres. Enrichment in muscle-skeletal tissues also appeared likely (**Supplementary Fig. 9**). Medium spiny neurons and pyramidal neurons from the CA1 region of the hippocampus were significantly associated with anorexia nervosa at a Bonferroni threshold in the 24 level 1 cell types (**Supplementary Fig. 10**). Among the 149 level 2 cell types, pyramidal neurons from the CA1 region of the hippocampus and pyramidal neurons from the somatosensory cortex layer 5 were Bonferroni-significant (**Supplementary Fig. 11**).

Medium spiny neurons (MSNs) are dopaminergic and inhibitory. They are the primary cell type of the striatum. The dorsal striatum has been linked to feeding behaviors including food motivation and reward[83]. D1R-medium-spiny-neurons (medium spiny neurons that express the D1-type dopamine receptor) afferents have been reported to be the primary source of nucleus accumbent inhibition to the lateral hypothalamus[84]. Furthermore, in that study, inhibition of D1R-MSNs increased feeding, while activation decreased feeding[84]. Pyramidal neurons are excitatory and are the primary excitatory cell type found in cortical structures[85]. Kim et al.[86] recently found that *PPP1R1B*-expressing pyramidal neurons from the

basolateral amygdala project to DR1-expressing central amygdala neurons, which are known to modulate appetitive behaviors.

Using the LDSC partitioned heritability approach[53], no significant signal was found in the GTEx database for tissues (**Supplementary Figs. 12-13**), in the Cahoy database for cells (**Supplementary Fig. 14**), or in the single-cell RNA-sequencing database (**Supplementary Fig. 15**). Nevertheless, in GTEx, the enrichment of heritability was more common in cell types in the brain, although enrichment in muscle-skeletal tissues was also evident, though no cell type reached significance (**Supplementary Fig. 13**). In the Cahoy database, the enrichment appeared more common in astrocytes compared with neurons and oligodendrocytes, although none of these reached statistical significance after Bonferroni correction (**Supplementary Fig. 14**). In the single-cell RNA-sequencing database, signal was strongest in neuroblasts (**Supplementary Fig. 15**).

3.3.15 Predicted tissue-specific gene expression

The PrediXcan analysis suggested significant effects on the expression of 36 genes across 44 GTEx tissues ($P \leq 1.94 \times 10^{-7}$; **Supplementary Table 13**). *MGMT* is located on chr10 (131.2-131.4 Mb). The majority of others are located within the multi-genic region on chr3. Downregulation and upregulation are presented in **Supplementary Table 13**.

3.3.16 Cross-trait analysis

3.3.17 Genetic correlations

Full results are shown in **Supplementary Table 10** and Bonferroni-significant results are shown graphically in **Fig. 2**. In instances where the same phenotype appears in multiple study sources, the main manuscript and **Fig. 2** report the result from the study source with the largest sample and/or of European ancestry.

3.3.18 Generalized summary data-based Mendelian randomization (GSMR)

BMI. We used GSMR[87] to investigate causal associations between BMI and anorexia nervosa using an extension of GCTA[57] (**Supplementary Table 16**). A one standard deviation (*SD*) decrease in genetically-estimated BMI increased the risk for anorexia nervosa by 4% (OR = 1.04; s.e. = 0.01; $P_{GSMR} = 0.008$) while an increase in genetically-estimated anorexia nervosa had a BMI-lowering effect ($b_{xy} = -0.28$, s.e. = 0.07, $P_{GSMR} = 5.15 \times 10^{-5}$). We only used eight SNPs to build the multiple SNP instrument for anorexia nervosa as an exposure and, hence, these results should be interpreted with caution.

To further separate effects of BMI from the anorexia nervosa phenotype, we used GCTA-mtCOJO[57,87] (multi-trait-based conditional & joint analysis using GWAS summary data) to adjust the anorexia nervosa GWAS summary statistics for BMI, using BMI summary statistics from our UK Biobank analysis, which excluded

individuals with a mental health diagnosis or taking a psychiatric or weight changing medication (see **Additional Methods**) and re-ran the GSMR analysis. The anorexia nervosa and BMI GWAS were performed on independent samples. As expected, after conditioning on BMI, the bidirectional pattern was no longer observable with $OR_{BMI \rightarrow AnorexiaNervosaAdjBMI}$ = 1.00 (s.e. = 0.01; P_{GSMR} = 0.78). However, the putative causal association from AnorexiaNervosaAdjBMI to BMI was still statistically significant (b_{xy} = -0.22, s.e. = 0.08, P_{GSMR} = 0.004). The results are consistent with a causal relationship not due to pleiotropy (in the case of the anorexia nervosa→BMI effect) between these two traits.

Type 2 diabetes. We also investigated the causal relationship between Type 2 diabetes and anorexia nervosa using GSMR. The association with Type 2 diabetes as an exposure and anorexia nervosa as an outcome was not statistically significant (bxy = -0.02, s.e. = 0.03, P_{GSMR} = 0.035), nor was the association with anorexia nervosa as an exposure and Type 2 diabetes as an outcome (bxy = -0.09, s.e. = 0.09, P_{GSMR} = 0.30). These results do not support either phenotype as having a putative causal effect on the other. The analysis with anorexia nervosa as an exposure had only 7 instrumental variables rather than the recommended minimum of 10, therefore results are to be interpreted cautiously and may change once the anorexia nervosa GWAS sample size increases.

3.3.19 References

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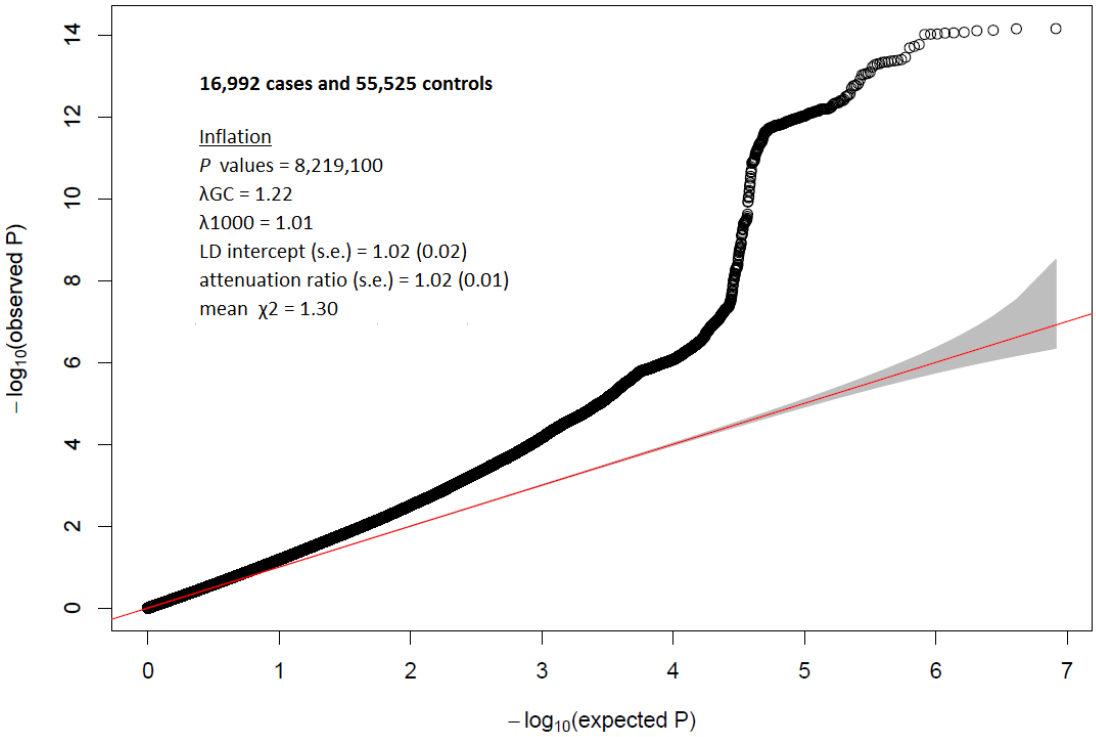
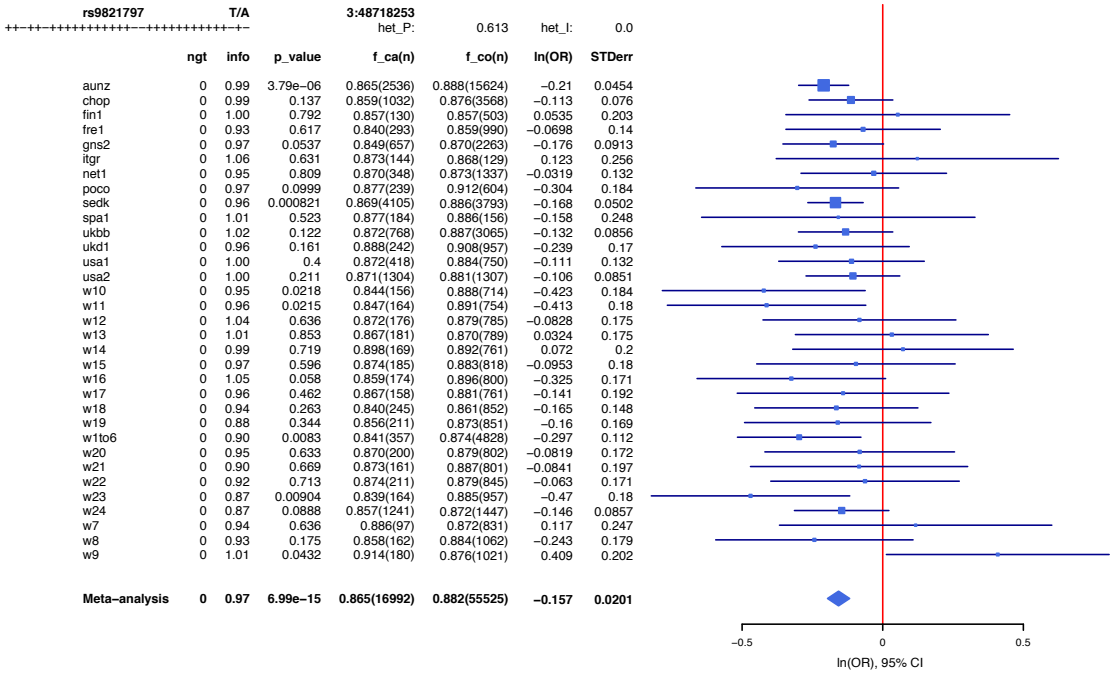
3.4 Supplementary Figures



Supplementary Figure 1. Quantile-quantile (QQ) plot of association P values for the meta-analysis of anorexia nervosa (MAF ≥ 0.01 and INFO score ≥ 0.70). The red diagonal line shows the theoretical null distribution. The shading shows the 95% confidence interval bounds. MAF = minor allele frequency and INFO = imputation quality score.

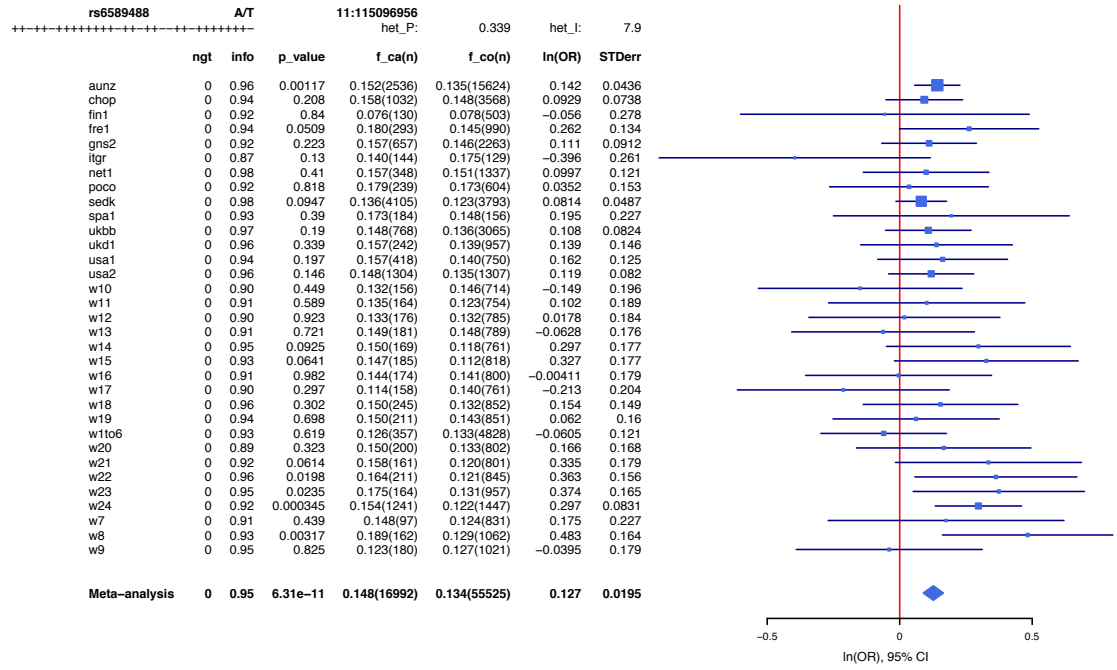
(a) chr3:rs9821797.



rs9821797	T/A		3:48718253			
			het_P:	0.613	het_I:	0.0

	ngt	info	p_value	f_ca(n)	f_co(n)	ln(OR)	STDerr
aunz	0	0.99	3.79e−06	0.865(2536)	0.888(15624)	−0.21	0.0454
chop	0	0.99	0.137	0.859(1032)	0.876(3568)	−0.113	0.076
fin1	0	1.00	0.792	0.857(130)	0.857(503)	0.0535	0.203
fre1	0	0.93	0.617	0.840(293)	0.859(990)	−0.0698	0.14
gns2	0	0.97	0.0537	0.849(657)	0.870(2263)	−0.176	0.0913
itgr	0	1.06	0.631	0.873(144)	0.868(129)	0.123	0.256
net1	0	0.95	0.809	0.870(348)	0.873(1337)	−0.0319	0.132
poco	0	0.97	0.0999	0.877(239)	0.912(604)	−0.304	0.184
sedk	0	0.96	0.000821	0.869(4105)	0.886(3793)	−0.168	0.0502
spa1	0	1.01	0.523	0.877(184)	0.886(156)	−0.158	0.248
ukbb	0	1.02	0.122	0.872(768)	0.887(3065)	−0.132	0.0856
ukd1	0	0.96	0.161	0.888(242)	0.908(957)	−0.239	0.17
usa1	0	1.00	0.4	0.872(418)	0.884(750)	−0.111	0.132
usa2	0	1.00	0.211	0.871(1304)	0.881(1307)	−0.106	0.0851
w10	0	0.95	0.0218	0.844(156)	0.888(714)	−0.423	0.184
w11	0	0.96	0.0215	0.847(164)	0.891(754)	−0.413	0.18
w12	0	1.04	0.636	0.872(176)	0.879(785)	−0.0828	0.175
w13	0	1.01	0.853	0.867(181)	0.870(789)	0.0324	0.175
w14	0	0.99	0.719	0.898(169)	0.892(761)	0.072	0.2
w15	0	0.97	0.596	0.874(185)	0.883(818)	−0.0953	0.18
w16	0	1.05	0.058	0.859(174)	0.896(800)	−0.325	0.171
w17	0	0.96	0.462	0.867(158)	0.881(761)	−0.141	0.192
w18	0	0.94	0.263	0.840(245)	0.861(852)	−0.165	0.148
w19	0	0.88	0.344	0.856(211)	0.873(851)	−0.16	0.169
w1to6	0	0.90	0.0083	0.841(357)	0.874(4828)	−0.297	0.112
w20	0	0.95	0.633	0.870(200)	0.879(802)	−0.0819	0.172
w21	0	0.90	0.669	0.873(161)	0.887(801)	−0.0841	0.197
w22	0	0.92	0.713	0.874(211)	0.879(845)	−0.063	0.171
w23	0	0.87	0.00904	0.839(164)	0.885(957)	−0.47	0.18
w24	0	0.87	0.0888	0.857(1241)	0.872(1447)	−0.146	0.0857
w7	0	0.94	0.636	0.886(97)	0.872(831)	0.117	0.247
w8	0	0.93	0.175	0.858(162)	0.884(1062)	−0.243	0.179
w9	0	1.01	0.0432	0.914(180)	0.876(1021)	0.409	0.202
Meta−analysis	**0**	**0.97**	**6.99e−15**	**0.865(16992)**	**0.882(55525)**	**−0.157**	**0.0201**

(b) chr11:6589488.

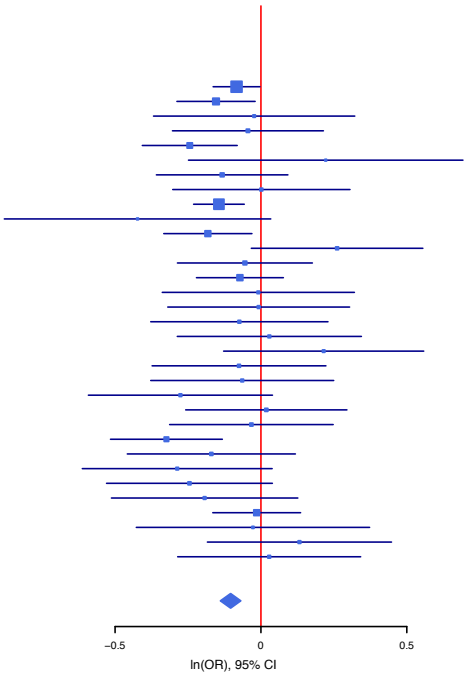


rs6589488	A/T		11:115096956			
			het_P:	0.339	het_I:	7.9

	ngt	info	p_value	f_ca(n)	f_co(n)	ln(OR)	STDerr
aunz	0	0.96	0.00117	0.152(2536)	0.135(15624)	0.142	0.0436
chop	0	0.94	0.208	0.158(1032)	0.148(3568)	0.0929	0.0738
fin1	0	0.92	0.84	0.076(130)	0.078(503)	−0.056	0.278
fre1	0	0.94	0.0509	0.180(293)	0.145(990)	0.262	0.134
gns2	0	0.92	0.223	0.157(657)	0.146(2263)	0.111	0.0912
itgr	0	0.87	0.13	0.140(144)	0.175(129)	−0.396	0.261
net1	0	0.98	0.41	0.157(348)	0.151(1337)	0.0997	0.121
poco	0	0.92	0.818	0.179(239)	0.173(604)	0.0352	0.153
sedk	0	0.98	0.0947	0.136(4105)	0.123(3793)	0.0814	0.0487
spa1	0	0.93	0.39	0.173(184)	0.148(156)	0.195	0.227
ukbb	0	0.97	0.19	0.148(768)	0.136(3065)	0.108	0.0824
ukd1	0	0.96	0.339	0.157(242)	0.139(957)	0.139	0.146
usa1	0	0.94	0.197	0.157(418)	0.140(750)	0.162	0.125
usa2	0	0.96	0.146	0.148(1304)	0.135(1307)	0.119	0.082
w10	0	0.90	0.449	0.132(156)	0.146(714)	−0.149	0.196
w11	0	0.91	0.589	0.135(164)	0.123(754)	0.102	0.189
w12	0	0.90	0.923	0.133(176)	0.132(785)	0.0178	0.184
w13	0	0.91	0.721	0.149(181)	0.148(789)	−0.0628	0.176
w14	0	0.95	0.0925	0.150(169)	0.118(761)	0.297	0.177
w15	0	0.93	0.0641	0.147(185)	0.112(818)	0.327	0.177
w16	0	0.91	0.982	0.144(174)	0.141(800)	−0.00411	0.179
w17	0	0.90	0.297	0.114(158)	0.140(761)	−0.213	0.204
w18	0	0.96	0.302	0.150(245)	0.132(852)	0.154	0.149
w19	0	0.94	0.698	0.150(211)	0.143(851)	0.062	0.16
w1to6	0	0.93	0.619	0.126(357)	0.133(4828)	−0.0605	0.121
w20	0	0.89	0.323	0.150(200)	0.133(802)	0.166	0.168
w21	0	0.92	0.0614	0.158(161)	0.120(801)	0.335	0.179
w22	0	0.96	0.0198	0.164(211)	0.121(845)	0.363	0.156
w23	0	0.95	0.0235	0.175(164)	0.131(957)	0.374	0.165
w24	0	0.92	0.000345	0.154(1241)	0.122(1447)	0.297	0.0831
w7	0	0.91	0.439	0.148(97)	0.124(831)	0.175	0.227
w8	0	0.93	0.00317	0.189(162)	0.129(1062)	0.483	0.164
w9	0	0.95	0.825	0.123(180)	0.127(1021)	−0.0395	0.179
Meta−analysis	**0**	**0.95**	**6.31e−11**	**0.148(16992)**	**0.134(55525)**	**0.127**	**0.0195**

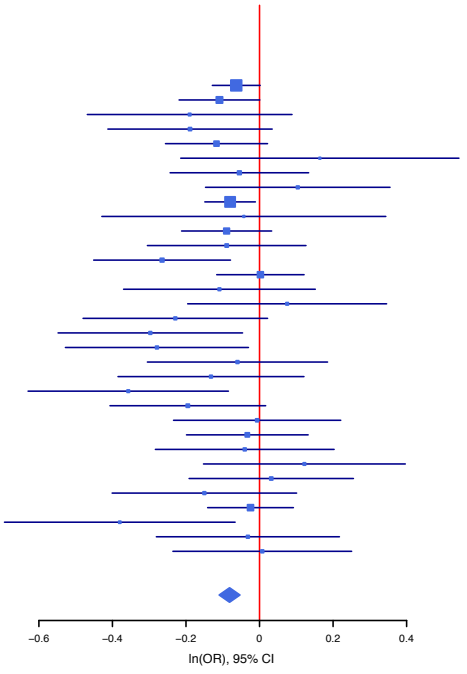
(c) chr2:2287348.

rs2287348		C/T		2:54039813			
				het_P:	0.309	het_I:	9.7
	ngt	**info**	**p_value**	**f_ca(n)**	**f_co(n)**	**ln(OR)**	**STDerr**
aunz	0	0.99	0.0412	0.830(2536)	0.843(15624)	−0.0836	0.041
chop	1	1.01	0.0244	0.822(1032)	0.845(3568)	−0.154	0.0684
fin1	1	1.01	0.894	0.796(130)	0.804(503)	−0.0233	0.176
fre1	0	0.99	0.735	0.834(293)	0.835(990)	−0.0446	0.132
gns2	0	0.98	0.00322	0.808(657)	0.845(2263)	−0.244	0.083
itgr	1	0.96	0.355	0.851(144)	0.818(129)	0.222	0.24
net1	1	0.97	0.247	0.816(348)	0.835(1337)	−0.133	0.115
poco	0	1.04	0.993	0.849(239)	0.839(604)	0.0014	0.155
sedk	0	0.99	0.00112	0.830(4105)	0.848(3793)	−0.144	0.0443
spa1	0	1.02	0.0693	0.824(184)	0.884(156)	−0.423	0.233
ukbb	1	1.00	0.0184	0.829(768)	0.853(3065)	−0.182	0.0771
ukd1	1	1.00	0.0823	0.872(242)	0.840(957)	0.261	0.15
usa1	1	0.99	0.64	0.830(418)	0.839(750)	−0.055	0.118
usa2	0	1.00	0.343	0.834(1304)	0.844(1307)	−0.0721	0.076
w10	0	1.02	0.958	0.833(156)	0.833(714)	−0.00894	0.168
w11	0	1.01	0.961	0.821(164)	0.823(754)	−0.00773	0.159
w12	0	1.02	0.634	0.826(176)	0.840(785)	−0.074	0.155
w13	0	1.02	0.858	0.845(181)	0.836(789)	0.0288	0.161
w14	0	1.05	0.219	0.873(169)	0.846(761)	0.215	0.175
w15	0	0.98	0.622	0.819(185)	0.825(818)	−0.0752	0.152
w16	0	1.00	0.688	0.828(174)	0.837(800)	−0.0642	0.16
w17	0	0.99	0.0858	0.791(158)	0.838(761)	−0.276	0.161
w18	0	0.99	0.896	0.841(245)	0.838(852)	0.0184	0.141
w19	0	1.01	0.819	0.822(211)	0.827(851)	−0.0327	0.143
w1to6	0	0.98	0.000925	0.792(357)	0.839(4828)	−0.324	0.0978
w20	0	1.05	0.247	0.828(200)	0.851(802)	−0.17	0.147
w21	0	0.99	0.0831	0.823(161)	0.856(801)	−0.287	0.166
w22	0	1.00	0.0899	0.820(211)	0.853(845)	−0.245	0.145
w23	0	0.95	0.237	0.821(164)	0.845(957)	−0.193	0.163
w24	0	0.97	0.85	0.843(1241)	0.845(1447)	−0.0146	0.0768
w7	0	1.00	0.893	0.825(97)	0.833(831)	−0.0274	0.204
w8	0	1.04	0.413	0.845(162)	0.825(1062)	0.132	0.161
w9	0	1.00	0.86	0.847(180)	0.844(1021)	0.0282	0.16
Meta−analysis	**7**	**0.99**	**5.62e−09**	**0.830(16992)**	**0.842(55525)**	**−0.104**	**0.0179**

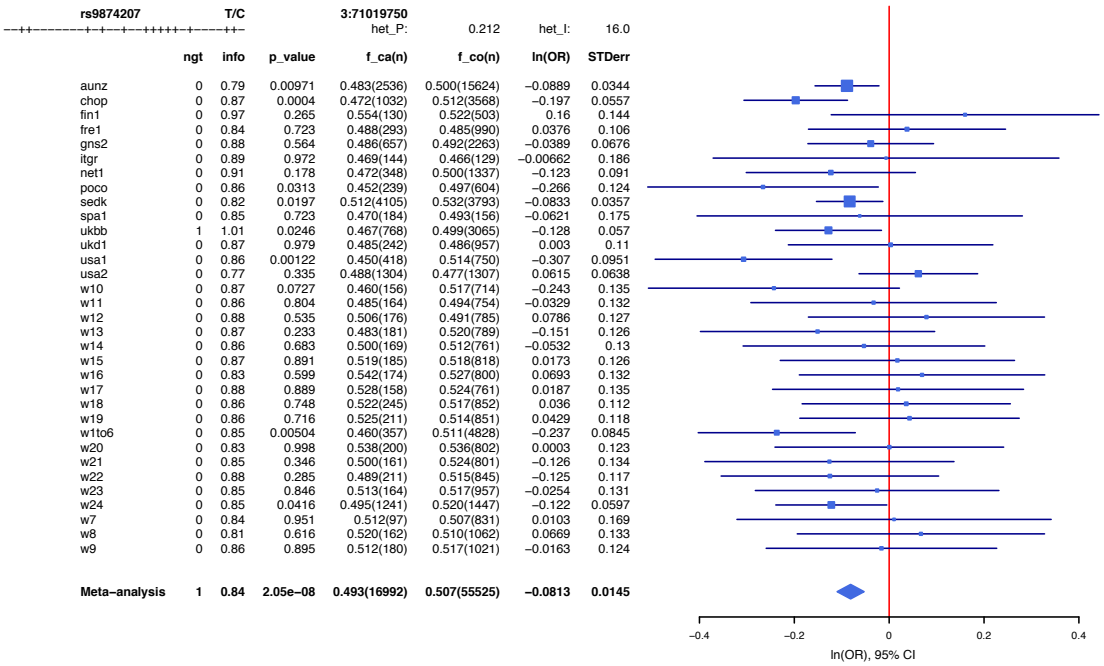


(d) chr10:rs2008387.

rs2008387		G/A		10:131448764			
				het_P:	0.358	het_I:	6.7
	ngt	**info**	**p_value**	**f_ca(n)**	**f_co(n)**	**ln(OR)**	**STDerr**
aunz	0	0.93	0.0565	0.650(2536)	0.663(15624)	−0.0633	0.0332
chop	0	0.93	0.0522	0.638(1032)	0.668(3568)	−0.109	0.056
fin1	0	1.01	0.182	0.556(130)	0.600(503)	−0.19	0.142
fre1	0	0.82	0.0967	0.653(293)	0.687(990)	−0.189	0.114
gns2	0	0.89	0.0999	0.653(657)	0.677(2263)	−0.117	0.0708
itgr	0	0.94	0.397	0.677(144)	0.642(129)	0.164	0.193
net1	0	0.93	0.569	0.680(348)	0.698(1337)	−0.0548	0.0961
poco	0	0.91	0.414	0.693(239)	0.661(604)	0.104	0.128
sedk	0	0.93	0.0226	0.645(4105)	0.661(3793)	−0.08	0.0351
spa1	0	0.77	0.829	0.677(184)	0.676(156)	−0.0427	0.197
ukbb	0	0.93	0.153	0.652(768)	0.670(3065)	−0.0895	0.0625
ukd1	0	0.97	0.416	0.653(242)	0.674(957)	−0.0893	0.11
usa1	0	0.93	0.0052	0.622(418)	0.674(750)	−0.265	0.0949
usa2	0	0.94	0.969	0.652(1304)	0.654(1307)	0.0024	0.0606
w10	0	0.99	0.413	0.643(156)	0.664(714)	−0.109	0.133
w11	0	0.92	0.586	0.692(164)	0.677(754)	0.0751	0.138
w12	0	0.95	0.0747	0.645(176)	0.696(785)	−0.229	0.128
w13	0	0.92	0.0199	0.620(181)	0.679(789)	−0.297	0.128
w14	0	0.99	0.0276	0.617(169)	0.681(761)	−0.279	0.127
w15	0	0.96	0.632	0.648(185)	0.665(818)	−0.06	0.125
w16	0	0.97	0.307	0.658(174)	0.681(800)	−0.132	0.129
w17	0	0.93	0.00996	0.635(158)	0.706(761)	−0.357	0.139
w18	0	0.99	0.0714	0.630(245)	0.675(852)	−0.195	0.108
w19	0	1.02	0.956	0.672(211)	0.671(851)	−0.00652	0.116
w1to6	0	0.95	0.693	0.666(357)	0.674(4828)	−0.0332	0.0844
w20	0	0.94	0.745	0.675(200)	0.683(802)	−0.0402	0.124
w21	0	0.93	0.383	0.706(161)	0.676(801)	0.122	0.14
w22	0	1.02	0.779	0.660(211)	0.653(845)	0.0319	0.114
w23	0	1.00	0.241	0.656(164)	0.685(957)	−0.15	0.128
w24	0	0.95	0.681	0.663(1241)	0.668(1447)	−0.0245	0.0595
w7	0	0.99	0.0175	0.598(97)	0.678(831)	−0.38	0.16
w8	0	1.02	0.803	0.682(162)	0.688(1062)	−0.0317	0.127
w9	0	0.98	0.952	0.667(180)	0.661(1021)	0.00747	0.124
Meta−analysis	**0**	**0.94**	**1.72e−08**	**0.651(16992)**	**0.670(55525)**	**−0.0815**	**0.0145**

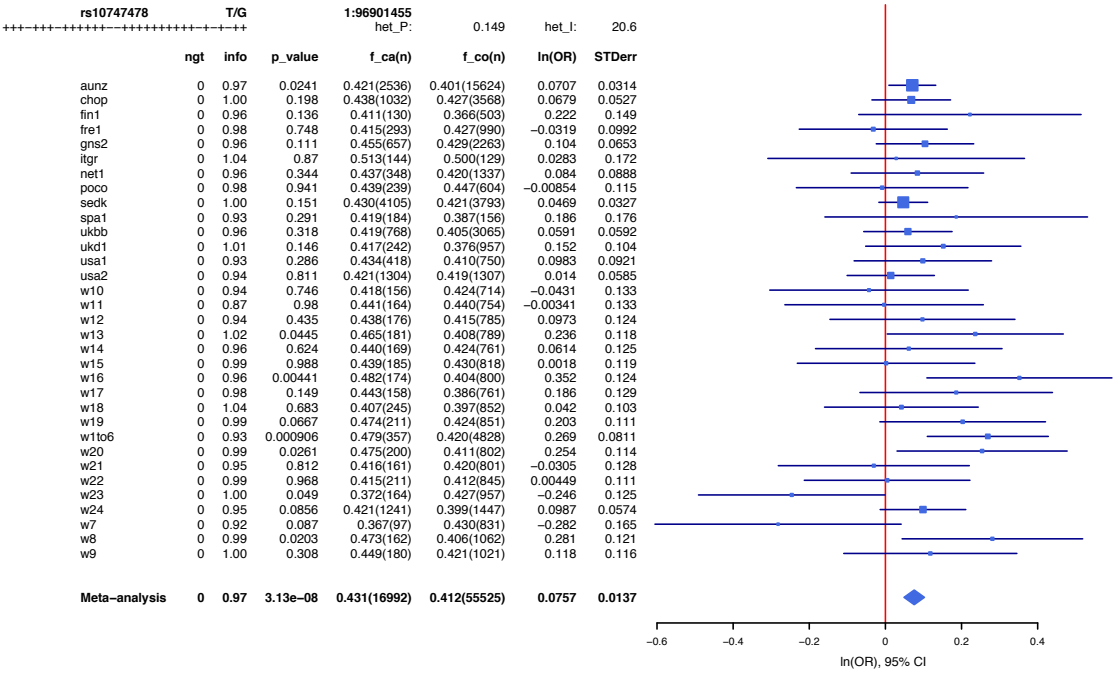


(e) chr3:rs9874207.



rs9874207	T/C		3:71019750			
			het_P:	0.212	het_I:	16.0
	ngt	info	p_value	f_ca(n)	f_co(n)	ln(OR)	STDerr
aunz	0	0.79	0.00971	0.483(2536)	0.500(15624)	−0.0889	0.0344
chop	0	0.87	0.0004	0.472(1032)	0.512(3568)	−0.197	0.0557
fin1	0	0.97	0.265	0.554(130)	0.522(503)	0.16	0.144
fre1	0	0.84	0.723	0.488(293)	0.485(990)	0.0376	0.106
gns2	0	0.88	0.564	0.486(657)	0.492(2263)	−0.0389	0.0676
itgr	0	0.89	0.972	0.469(144)	0.466(129)	−0.00662	0.186
net1	0	0.91	0.178	0.472(348)	0.500(1337)	−0.123	0.091
poco	0	0.86	0.0313	0.452(239)	0.497(604)	−0.266	0.124
sedk	0	0.82	0.0197	0.512(4105)	0.532(3793)	−0.0833	0.0357
spa1	0	0.85	0.723	0.470(184)	0.493(156)	−0.0621	0.175
ukbb	1	1.01	0.0246	0.467(768)	0.499(3065)	−0.128	0.057
ukd1	0	0.87	0.979	0.485(242)	0.486(957)	0.003	0.11
usa1	0	0.86	0.00122	0.450(418)	0.514(750)	−0.307	0.0951
usa2	0	0.77	0.335	0.488(1304)	0.477(1307)	0.0615	0.0638
w10	0	0.87	0.0727	0.460(156)	0.517(714)	−0.243	0.135
w11	0	0.86	0.804	0.485(164)	0.494(754)	−0.0329	0.132
w12	0	0.88	0.535	0.506(176)	0.491(785)	0.0786	0.127
w13	0	0.87	0.233	0.483(181)	0.520(789)	−0.151	0.126
w14	0	0.86	0.683	0.500(169)	0.512(761)	−0.0532	0.13
w15	0	0.87	0.891	0.519(185)	0.518(818)	0.0173	0.126
w16	0	0.83	0.599	0.542(174)	0.527(800)	0.0693	0.132
w17	0	0.88	0.889	0.528(158)	0.524(761)	0.0187	0.135
w18	0	0.86	0.748	0.522(245)	0.517(852)	0.036	0.112
w19	0	0.86	0.716	0.525(211)	0.514(851)	0.0429	0.118
w1to6	0	0.85	0.00504	0.460(357)	0.511(4828)	−0.237	0.0845
w20	0	0.83	0.998	0.538(200)	0.536(802)	0.0003	0.123
w21	0	0.85	0.346	0.500(161)	0.524(801)	−0.126	0.134
w22	0	0.88	0.285	0.489(211)	0.515(845)	−0.125	0.117
w23	0	0.85	0.846	0.513(164)	0.517(957)	−0.0254	0.131
w24	0	0.85	0.0416	0.495(1241)	0.520(1447)	−0.122	0.0597
w7	0	0.84	0.951	0.512(97)	0.507(831)	0.0103	0.169
w8	0	0.81	0.616	0.520(162)	0.510(1062)	0.0669	0.133
w9	0	0.86	0.895	0.512(180)	0.517(1021)	−0.0163	0.124
Meta−analysis	**1**	**0.84**	**2.05e−08**	**0.493(16992)**	**0.507(55525)**	**−0.0813**	**0.0145**

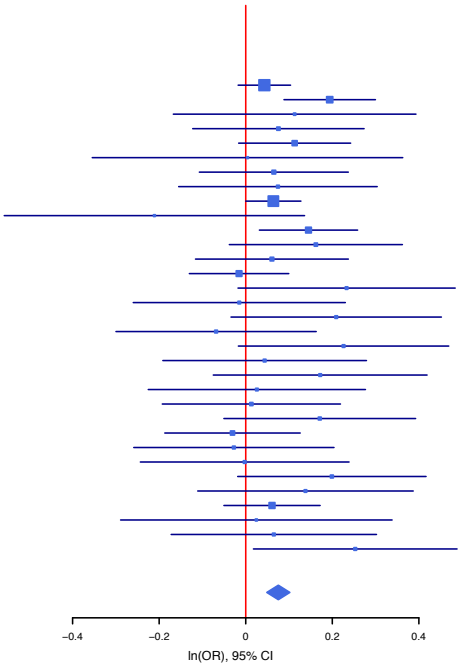
(f) chr1:rs10747478.



rs10747478	T/G		1:96901455			
			het_P:	0.149	het_I:	20.6
	ngt	info	p_value	f_ca(n)	f_co(n)	ln(OR)	STDerr
aunz	0	0.97	0.0241	0.421(2536)	0.401(15624)	0.0707	0.0314
chop	0	1.00	0.198	0.438(1032)	0.427(3568)	0.0679	0.0527
fin1	0	0.96	0.136	0.411(130)	0.366(503)	0.222	0.149
fre1	0	0.98	0.748	0.415(293)	0.427(990)	−0.0319	0.0992
gns2	0	0.96	0.111	0.455(657)	0.429(2263)	0.104	0.0653
itgr	0	1.04	0.87	0.513(144)	0.500(129)	0.0283	0.172
net1	0	0.96	0.344	0.437(348)	0.420(1337)	0.084	0.0888
poco	0	0.98	0.941	0.439(239)	0.447(604)	−0.00854	0.115
sedk	0	1.00	0.151	0.430(4105)	0.421(3793)	0.0469	0.0327
spa1	0	0.93	0.291	0.419(184)	0.387(156)	0.186	0.176
ukbb	0	0.96	0.318	0.419(768)	0.405(3065)	0.0591	0.0592
ukd1	0	1.01	0.146	0.417(242)	0.376(957)	0.152	0.104
usa1	0	0.93	0.286	0.434(418)	0.410(750)	0.0983	0.0921
usa2	0	0.94	0.811	0.421(1304)	0.419(1307)	0.014	0.0585
w10	0	0.94	0.746	0.418(156)	0.424(714)	−0.0431	0.133
w11	0	0.87	0.98	0.441(164)	0.440(754)	−0.00341	0.133
w12	0	0.94	0.435	0.438(176)	0.415(785)	0.0973	0.124
w13	0	1.02	0.0445	0.465(181)	0.408(789)	0.236	0.118
w14	0	0.96	0.624	0.440(169)	0.424(761)	0.0614	0.125
w15	0	0.99	0.988	0.439(185)	0.430(818)	0.0018	0.119
w16	0	0.96	0.00441	0.482(174)	0.404(800)	0.352	0.124
w17	0	0.98	0.149	0.443(158)	0.386(761)	0.186	0.129
w18	0	1.04	0.683	0.407(245)	0.397(852)	0.042	0.103
w19	0	0.99	0.0667	0.474(211)	0.424(851)	0.203	0.111
w1to6	0	0.93	0.000906	0.479(357)	0.420(4828)	0.269	0.0811
w20	0	0.99	0.0261	0.475(200)	0.411(802)	0.254	0.114
w21	0	0.95	0.812	0.416(161)	0.420(801)	−0.0305	0.128
w22	0	0.99	0.968	0.415(211)	0.412(845)	0.00449	0.111
w23	0	1.00	0.049	0.372(164)	0.427(957)	−0.246	0.125
w24	0	0.95	0.0856	0.421(1241)	0.399(1447)	0.0987	0.0574
w7	0	0.92	0.087	0.367(97)	0.430(831)	−0.282	0.165
w8	0	0.99	0.0203	0.473(162)	0.406(1062)	0.281	0.121
w9	0	1.00	0.308	0.449(180)	0.421(1021)	0.118	0.116
Meta−analysis	**0**	**0.97**	**3.13e−08**	**0.431(16992)**	**0.412(55525)**	**0.0757**	**0.0137**

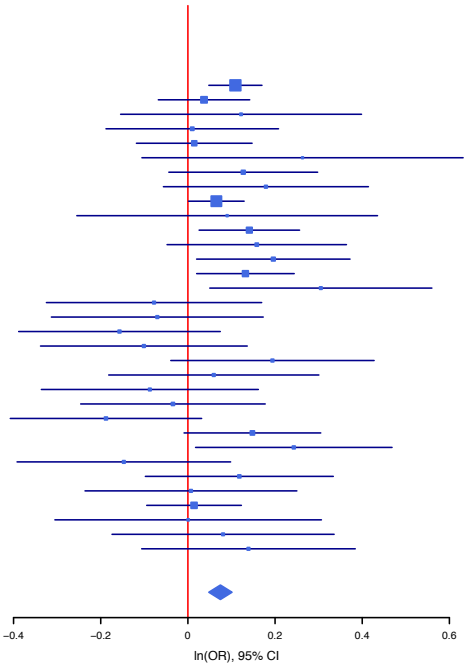
(g) chr5:rs370838138.

rs370838138		G/C		5:25081845			
				het_P:	0.637	het_I:	0.0
	ngt	info	p_value	f_ca(n)	f_co(n)	ln(OR)	STDerr
aunz	0	0.99	0.164	0.574(2536)	0.560(15624)	0.043	0.0309
chop	0	0.99	0.000315	0.607(1032)	0.563(3568)	0.194	0.0539
fin1	0	0.99	0.429	0.535(130)	0.504(503)	0.113	0.143
fre1	0	0.98	0.455	0.617(293)	0.589(990)	0.0755	0.101
gns2	0	0.95	0.0855	0.590(657)	0.563(2263)	0.113	0.066
itgr	0	0.97	0.982	0.625(144)	0.629(129)	0.00409	0.183
net1	0	1.02	0.46	0.597(348)	0.576(1337)	0.0649	0.0878
poco	0	0.92	0.527	0.546(239)	0.520(604)	0.0744	0.117
sedk	0	1.00	0.0499	0.563(4105)	0.548(3793)	0.0638	0.0325
spa1	0	0.93	0.233	0.609(184)	0.664(156)	−0.211	0.177
ukbb	0	1.01	0.0125	0.592(768)	0.555(3065)	0.145	0.0579
ukd1	0	1.04	0.11	0.578(242)	0.535(957)	0.162	0.102
usa1	0	0.96	0.502	0.588(418)	0.567(750)	0.0605	0.0901
usa2	0	0.95	0.793	0.586(1304)	0.592(1307)	−0.0154	0.0586
w10	0	1.03	0.0683	0.618(156)	0.559(714)	0.233	0.128
w11	0	0.98	0.905	0.568(164)	0.575(754)	−0.0149	0.125
w12	0	0.97	0.0919	0.614(176)	0.565(785)	0.209	0.124
w13	0	1.00	0.563	0.549(181)	0.567(789)	−0.0685	0.118
w14	0	1.02	0.0676	0.622(169)	0.570(761)	0.226	0.124
w15	0	0.95	0.716	0.572(185)	0.562(818)	0.0437	0.12
w16	0	0.96	0.174	0.614(174)	0.573(800)	0.172	0.126
w17	0	0.96	0.841	0.576(158)	0.559(761)	0.0257	0.128
w18	0	0.98	0.902	0.564(245)	0.563(852)	0.013	0.105
w19	0	0.99	0.131	0.614(211)	0.575(851)	0.171	0.113
w1to6	0	0.96	0.702	0.571(357)	0.579(4828)	−0.0306	0.0798
w20	0	0.93	0.816	0.586(200)	0.591(802)	−0.0274	0.118
w21	0	1.04	0.984	0.591(161)	0.590(801)	−0.0024	0.123
w22	0	1.03	0.0724	0.617(211)	0.569(845)	0.199	0.111
w23	0	0.93	0.278	0.595(164)	0.564(957)	0.138	0.127
w24	0	0.96	0.284	0.589(1241)	0.574(1447)	0.0607	0.0567
w7	0	0.93	0.879	0.555(97)	0.558(831)	0.0245	0.16
w8	0	1.00	0.592	0.577(162)	0.562(1062)	0.0649	0.121
w9	0	0.98	0.0358	0.633(180)	0.572(1021)	0.253	0.12
Meta−analysis	**0**	**0.98**	**3.17e−08**	**0.582(16992)**	**0.564(55525)**	**0.0753**	**0.0136**



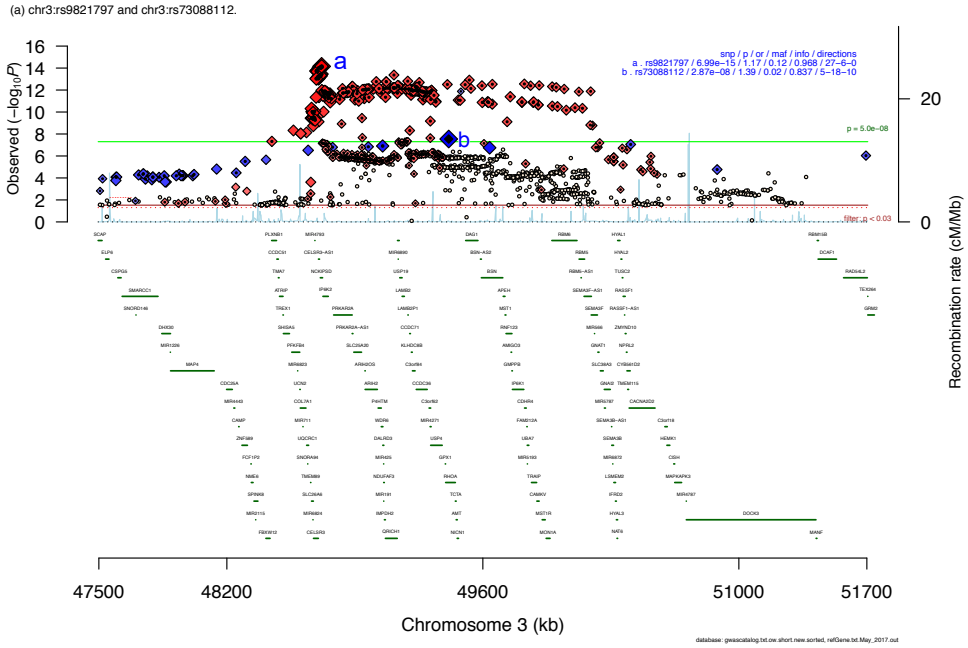
(h) chr3:rs13100344.

rs13100344		T/A		3:94605107			
				het_P:	0.175	het_I:	18.6
	ngt	info	p_value	f_ca(n)	f_co(n)	ln(OR)	STDerr
aunz	0	0.98	0.000439	0.564(2536)	0.536(15624)	0.109	0.0311
chop	0	0.95	0.489	0.545(1032)	0.541(3568)	0.037	0.0535
fin1	0	1.03	0.388	0.482(130)	0.448(503)	0.122	0.141
fre1	0	0.93	0.921	0.535(293)	0.524(990)	0.01	0.101
gns2	0	0.88	0.829	0.530(657)	0.526(2263)	0.0146	0.0677
itgr	0	0.94	0.162	0.626(144)	0.580(129)	0.263	0.188
net1	0	1.00	0.145	0.534(348)	0.505(1337)	0.127	0.0871
poco	0	0.91	0.135	0.581(239)	0.535(604)	0.179	0.12
sedk	0	0.99	0.0447	0.530(4105)	0.513(3793)	0.0653	0.0325
spa1	0	0.86	0.608	0.550(184)	0.541(156)	0.0901	0.176
ukbb	0	0.97	0.0162	0.581(768)	0.547(3065)	0.141	0.0588
ukd1	0	0.98	0.131	0.585(242)	0.549(957)	0.158	0.105
usa1	0	0.97	0.0291	0.580(418)	0.528(750)	0.196	0.0898
usa2	0	0.97	0.021	0.567(1304)	0.538(1307)	0.132	0.0571
w10	0	0.99	0.0194	0.617(156)	0.547(714)	0.305	0.13
w11	0	0.96	0.539	0.535(164)	0.554(754)	−0.0777	0.126
w12	0	0.92	0.57	0.517(176)	0.534(785)	−0.0702	0.124
w13	0	1.02	0.184	0.513(181)	0.553(789)	−0.157	0.118
w14	0	1.00	0.404	0.528(169)	0.552(761)	−0.101	0.121
w15	0	0.98	0.104	0.582(185)	0.535(818)	0.194	0.119
w16	0	0.97	0.63	0.572(174)	0.553(800)	0.0594	0.123
w17	0	0.98	0.49	0.521(158)	0.543(761)	−0.0873	0.127
w18	0	0.92	0.752	0.526(245)	0.532(852)	−0.0343	0.108
w19	0	0.97	0.0935	0.531(211)	0.571(851)	−0.188	0.112
w1to6	0	0.98	0.0646	0.586(357)	0.551(4828)	0.148	0.08
w20	0	0.98	0.0342	0.574(200)	0.514(802)	0.243	0.115
w21	0	0.98	0.24	0.521(161)	0.553(801)	−0.147	0.125
w22	0	1.00	0.284	0.561(211)	0.535(845)	0.118	0.11
w23	0	0.97	0.955	0.535(164)	0.541(957)	0.00698	0.124
w24	0	0.99	0.8	0.556(1241)	0.553(1447)	0.0141	0.0554
w7	0	0.99	0.997	0.557(97)	0.557(831)	0.0006	0.156
w8	0	0.86	0.534	0.555(162)	0.539(1062)	0.0807	0.13
w9	0	0.86	0.268	0.566(180)	0.536(1021)	0.139	0.125
Meta−analysis	**0**	**0.96**	**4.21e−08**	**0.551(16992)**	**0.537(55525)**	**0.0746**	**0.0136**

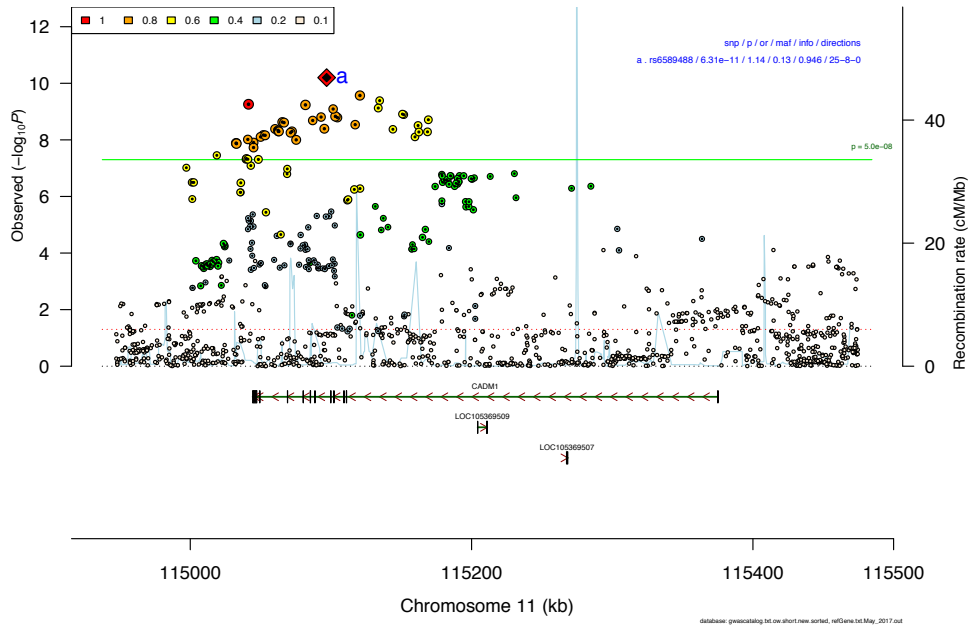


Supplementary Figure 2a-h legend. Forest plots of GWAS meta-analysis results for all genome-wide significant SNPs (P < 5 × 10-8). The overall sample size is 16,992 cases and 55,525 controls. For specific cohort sample sizes, see

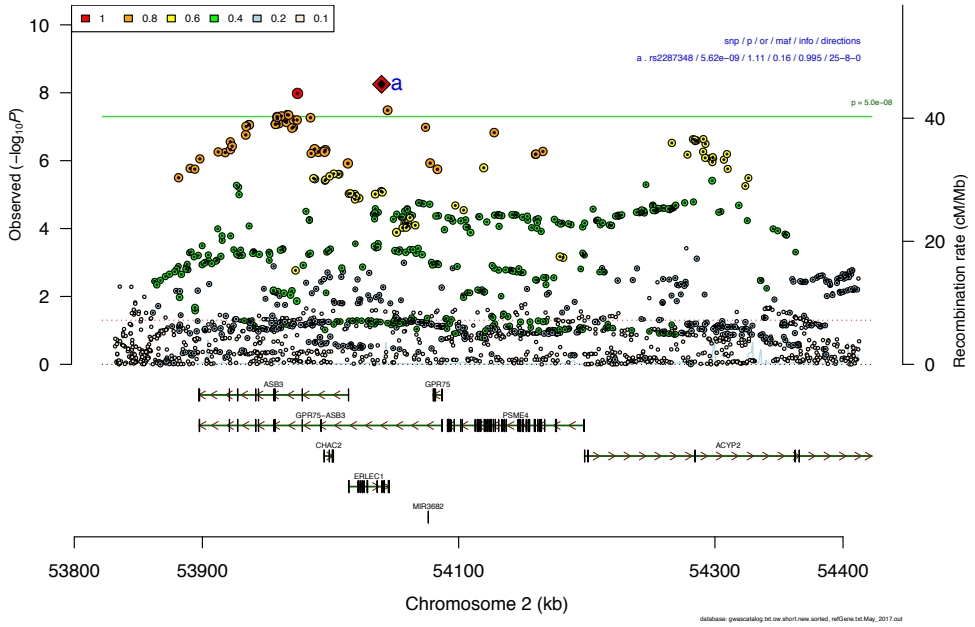
Supplementary Table 1. Two SNPs were located in regions that overlapped (index SNPs of rs9821797 and rs73088112), therefore we refer to only one of these (rs9821797) in the main manuscript. The red vertical line is the reference line of no effect. The center values are ln(OR) estimates from logistic regression association analyses and the error bars show the 95% confidence interval.



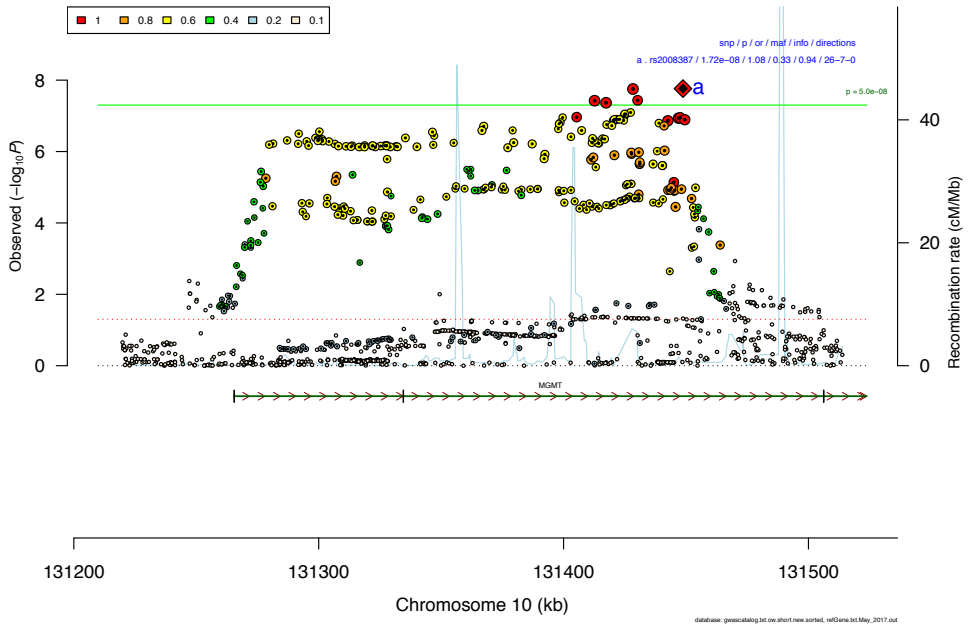
(b) chr11:6589488.



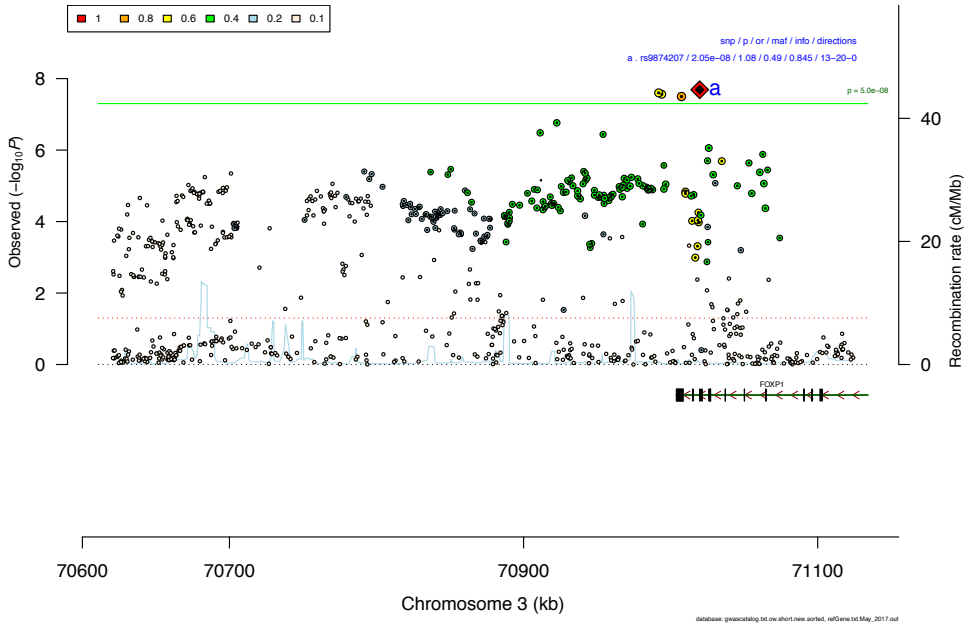
(c) chr2:2287348.



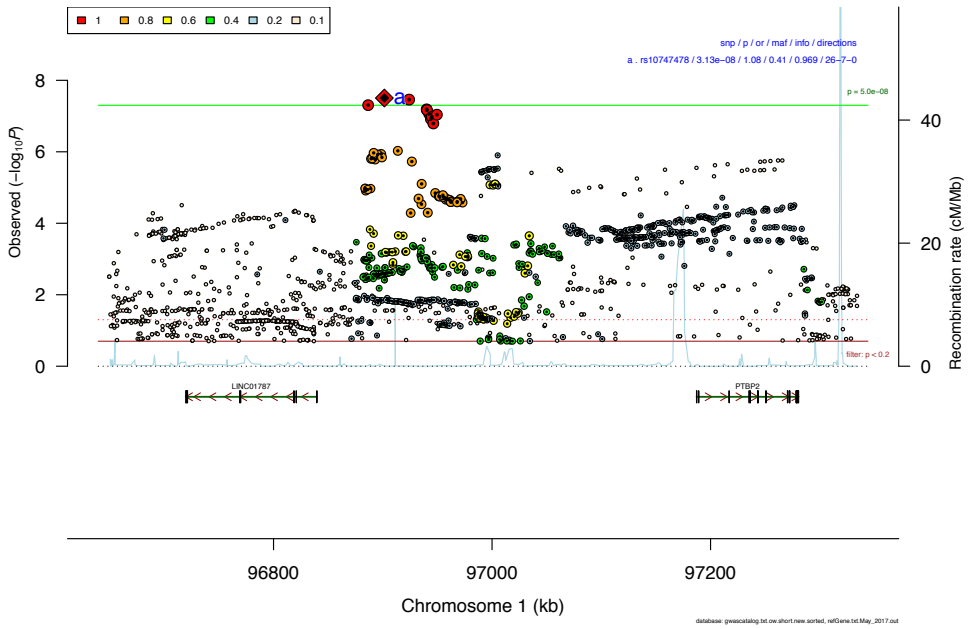
(d) chr10:rs2008387.



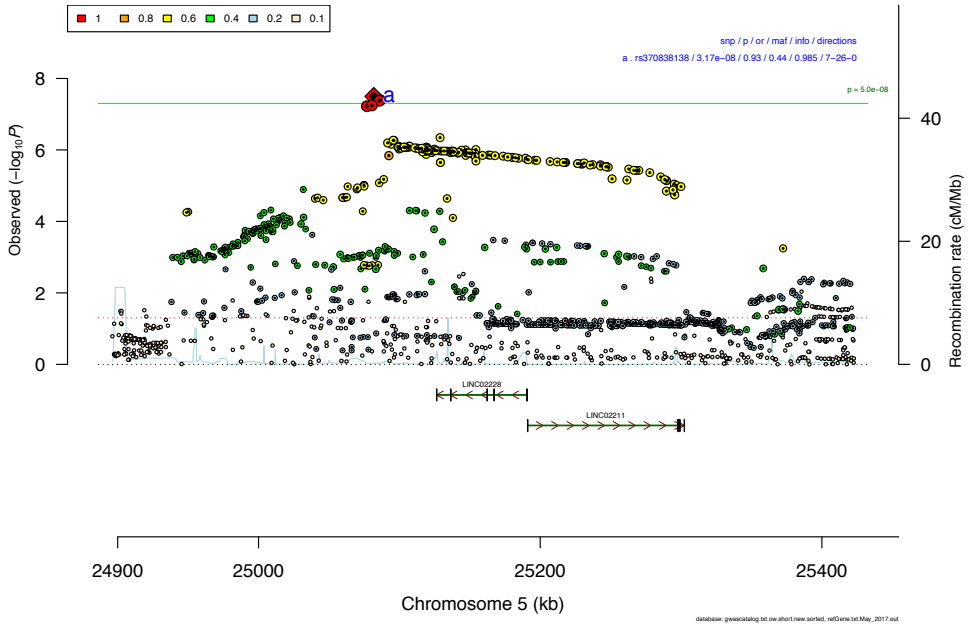
(e) chr3:rs9874207.

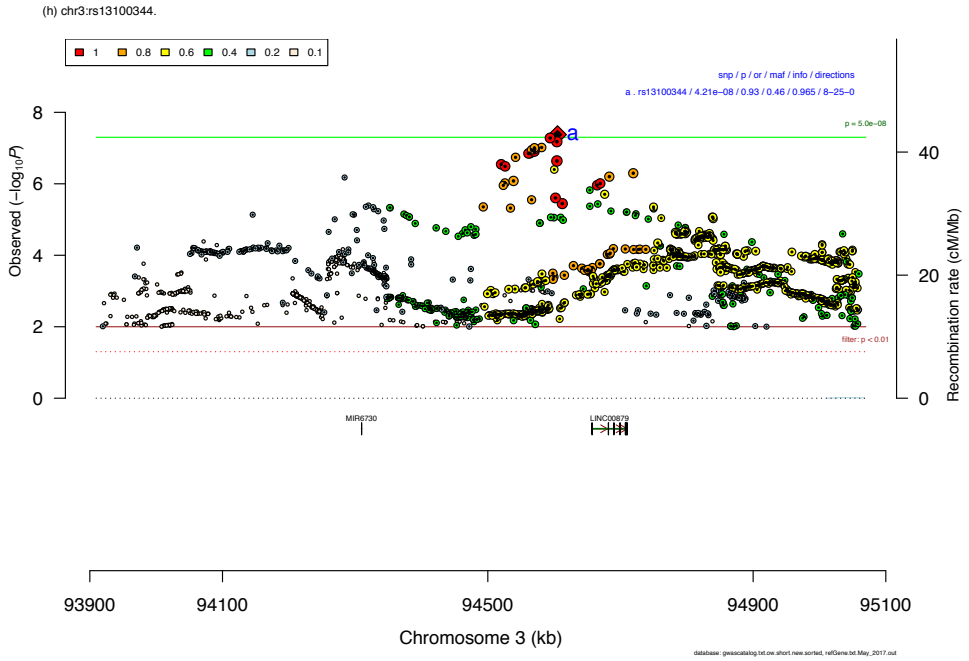


(f) chr1:rs10747478.

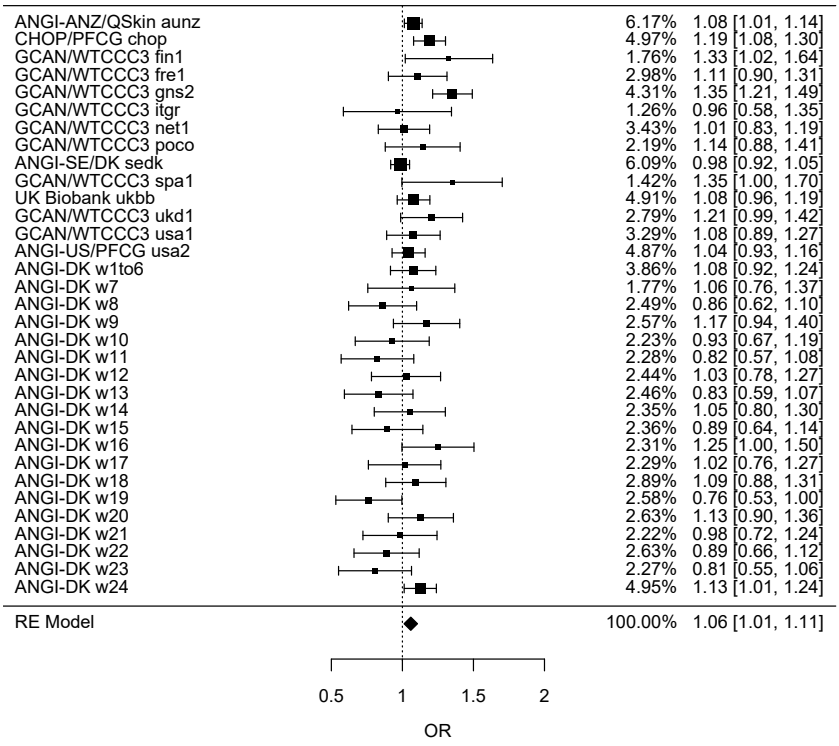


(g) chr5:rs370838138.



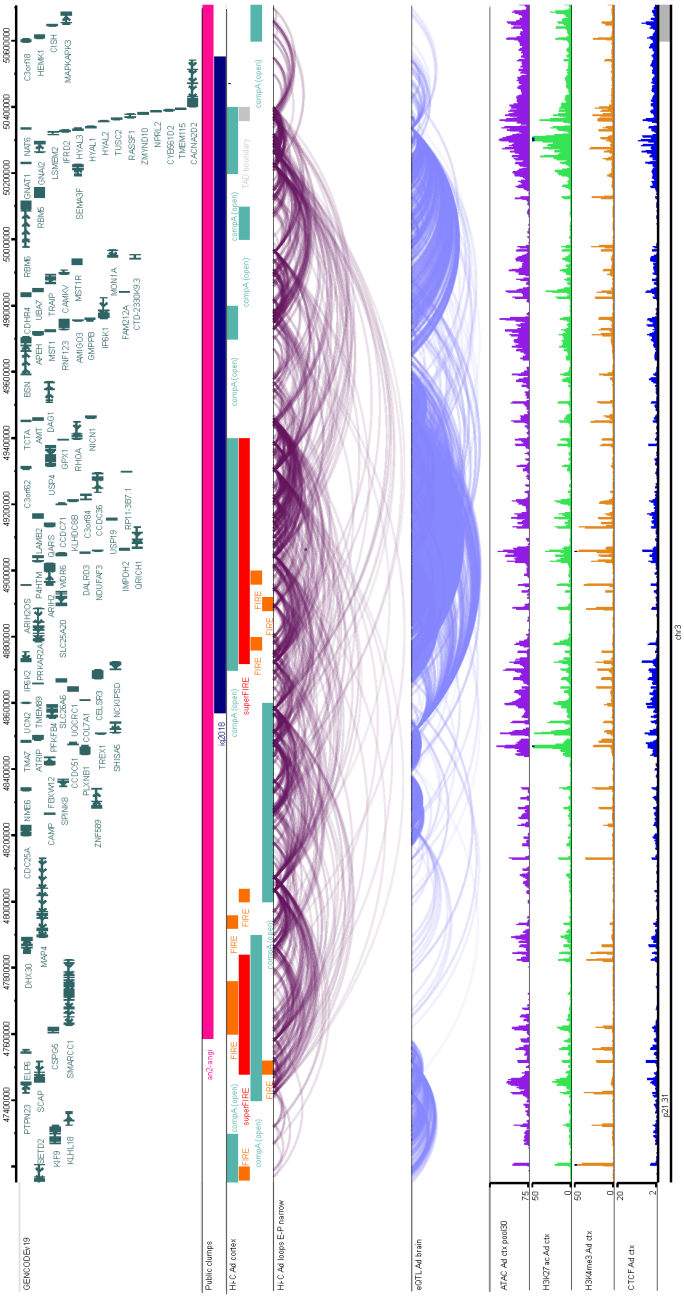


Supplementary Figure 3a-h legend. Regional plot of GWAS meta-analysis results for all genome-wide significant loci. The sample size is 16,992 cases and 55,525 controls. Two loci overlapped (index SNPs of rs9821797 and rs73088112), therefore we refer to only one of these (rs9821797) in the main manuscript.

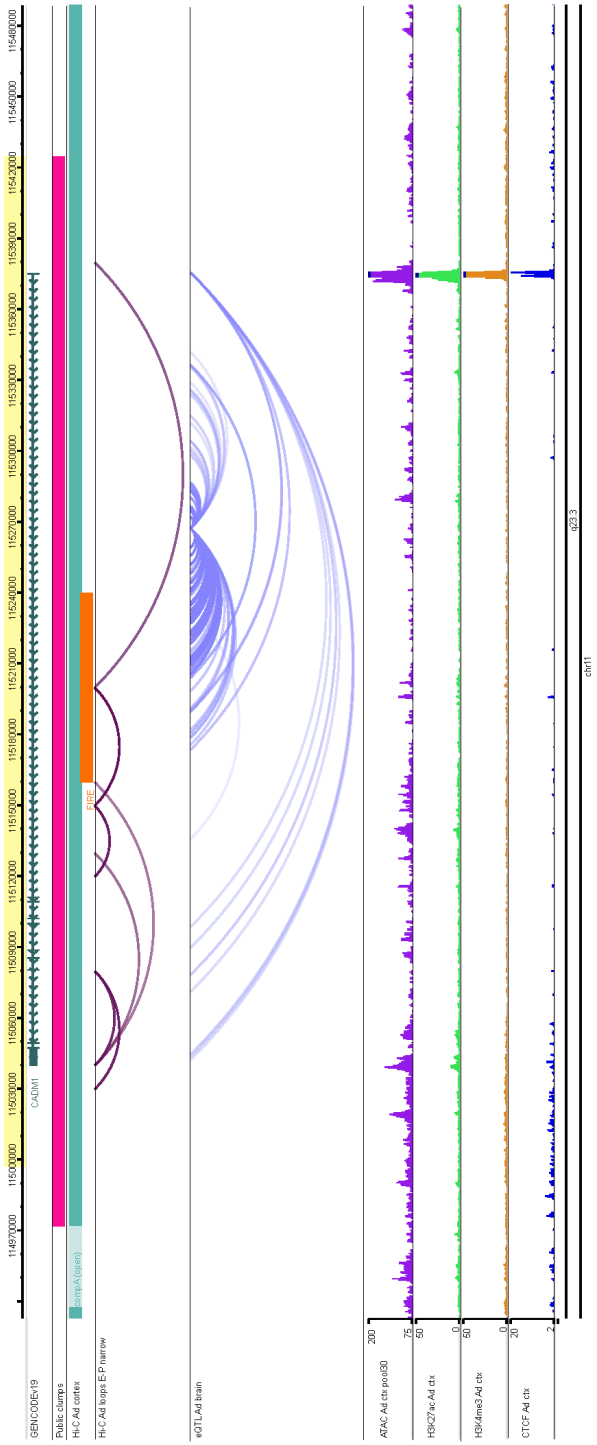


Supplementary Figure 4. A random-effects meta-analysis of the association between rs4622308 and anorexia nervosa. Previously, the first freeze of the PGC-ED revealed that this SNP was genome-wide significant (Duncan et al., 2017). In the present study, this SNP was not genome-wide significant in the primary GWAS meta-analysis using a fixed-effects model, and in a subsequent random effects meta-analysis as shown in this figure was also non-significant and showed evidence of heterogeneity (odds ratio [OR] = 1.06, 95% CI = 1.01-1.11, Ptwo-tailed = 0.0002, I2 = 53.76). The percentages refer to the weight assigned to each cohort. The figures on the right are the percentage weight assigned to each cohort, the center values are the OR, and the error bar is the 95% confidence interval. The vertical line is the reference line of no effect. The sample size is 16,992 cases and 55,525 controls.

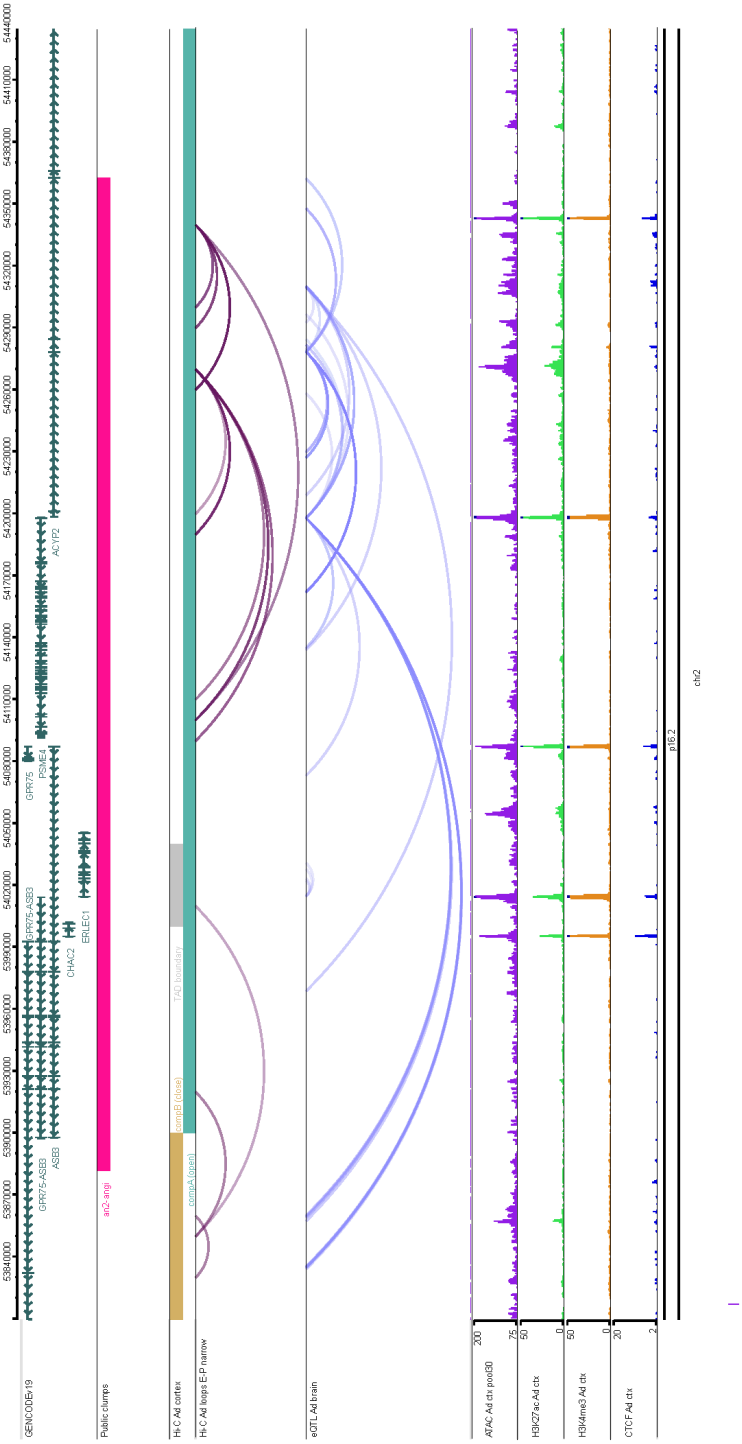
Supplementary Figure 5a



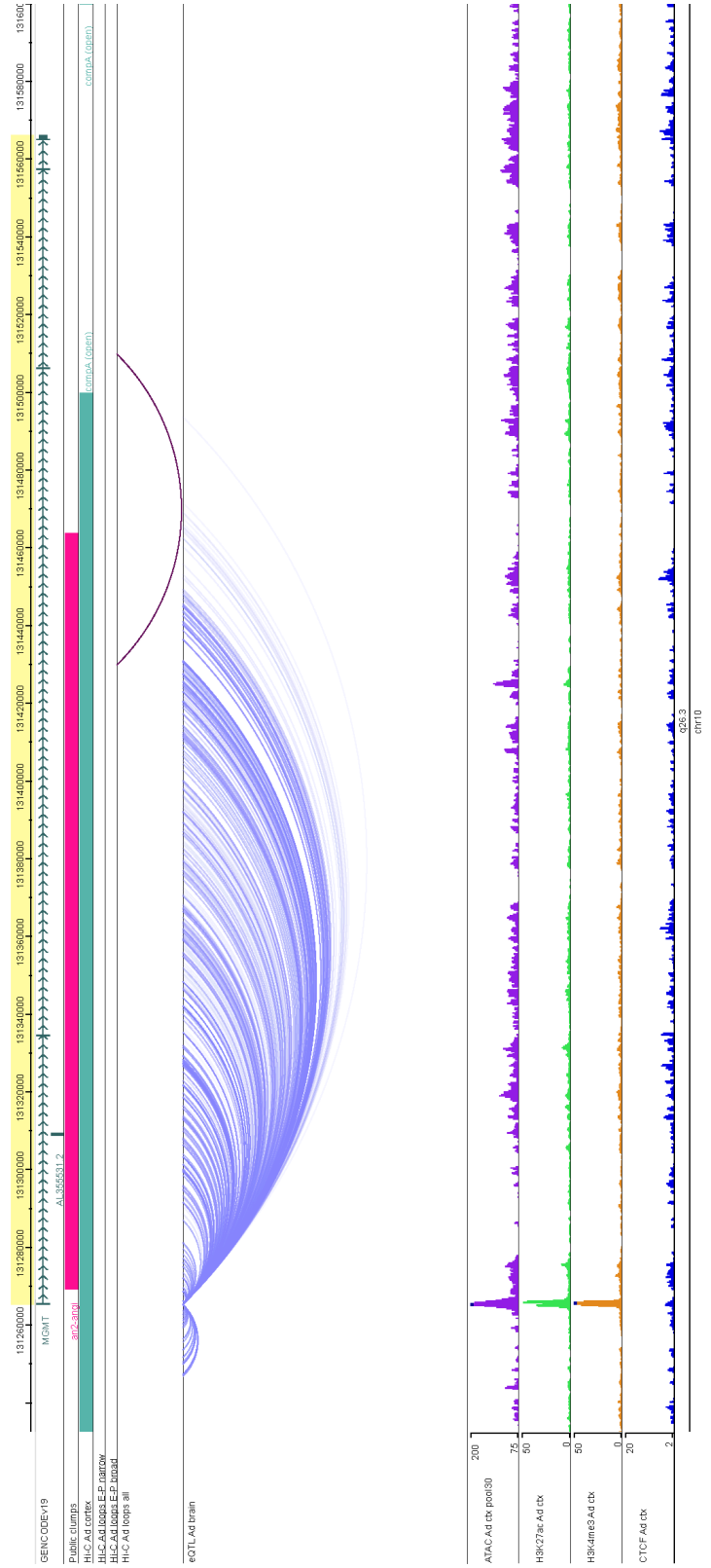
Supplementary Figure 5b



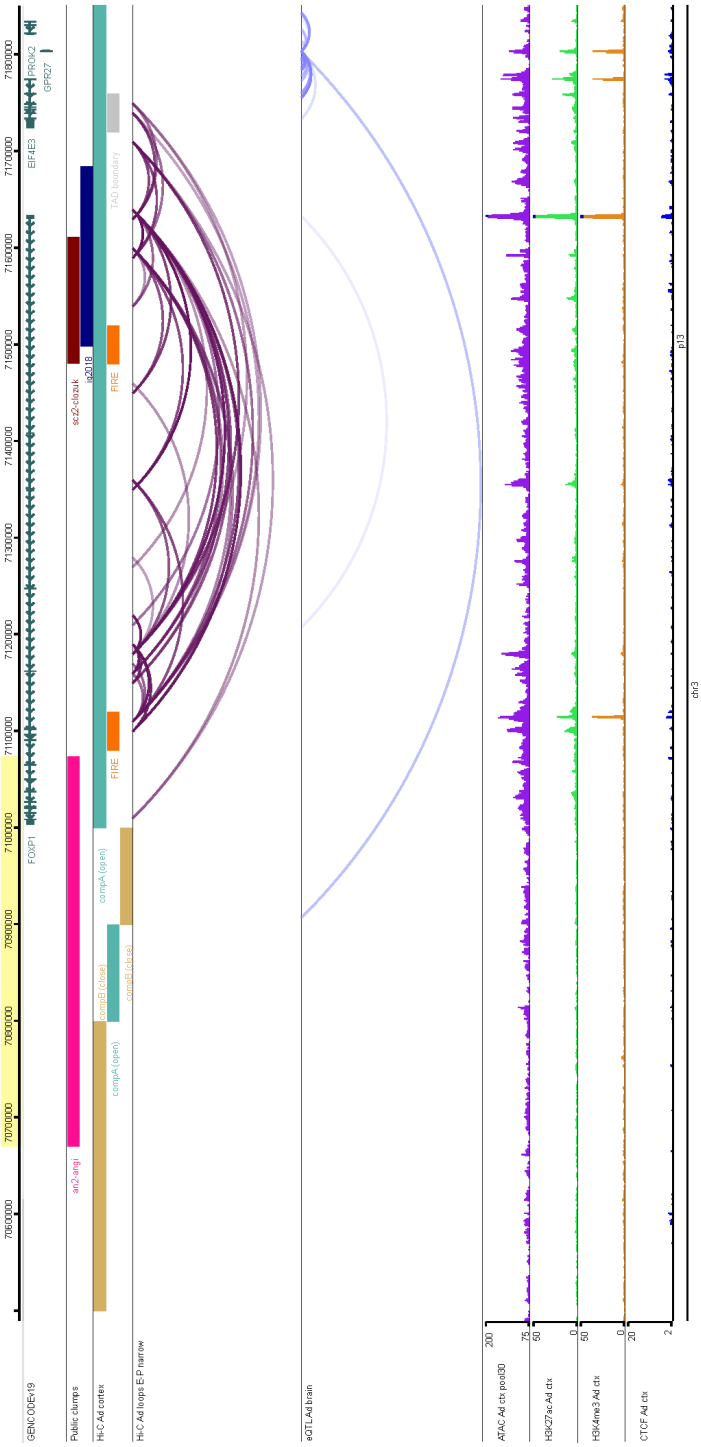
Supplementary Figure 5c



Supplementary Figure 5d



Supplementary Figure 5e



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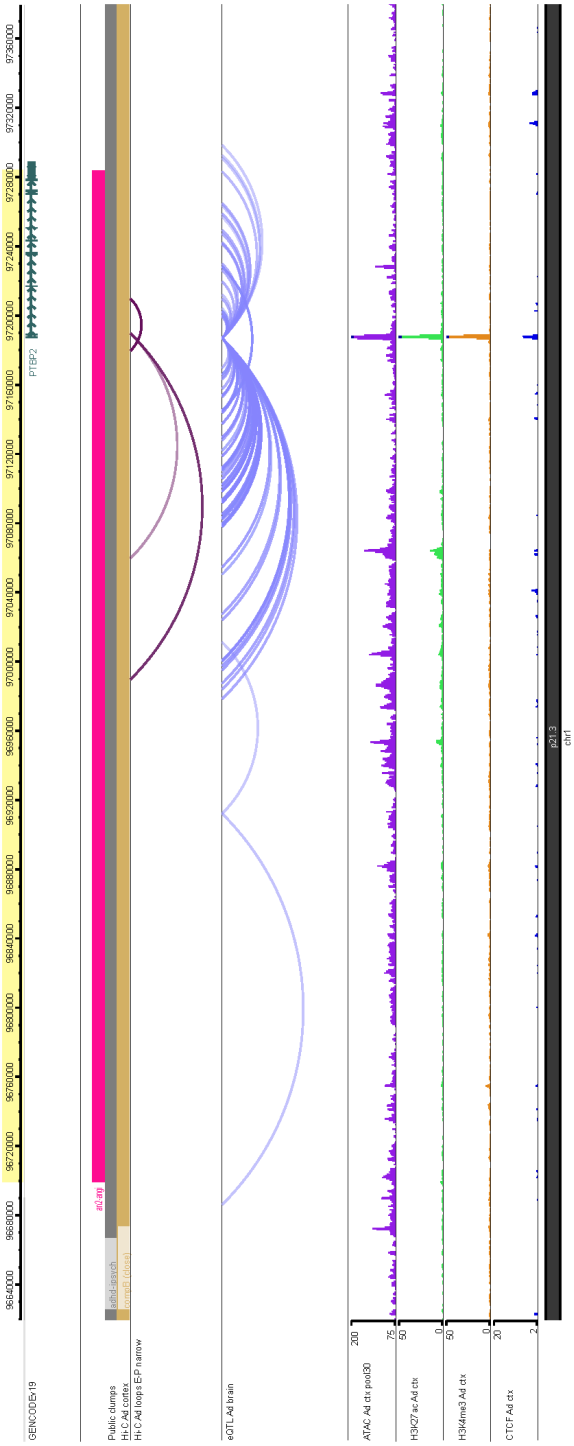

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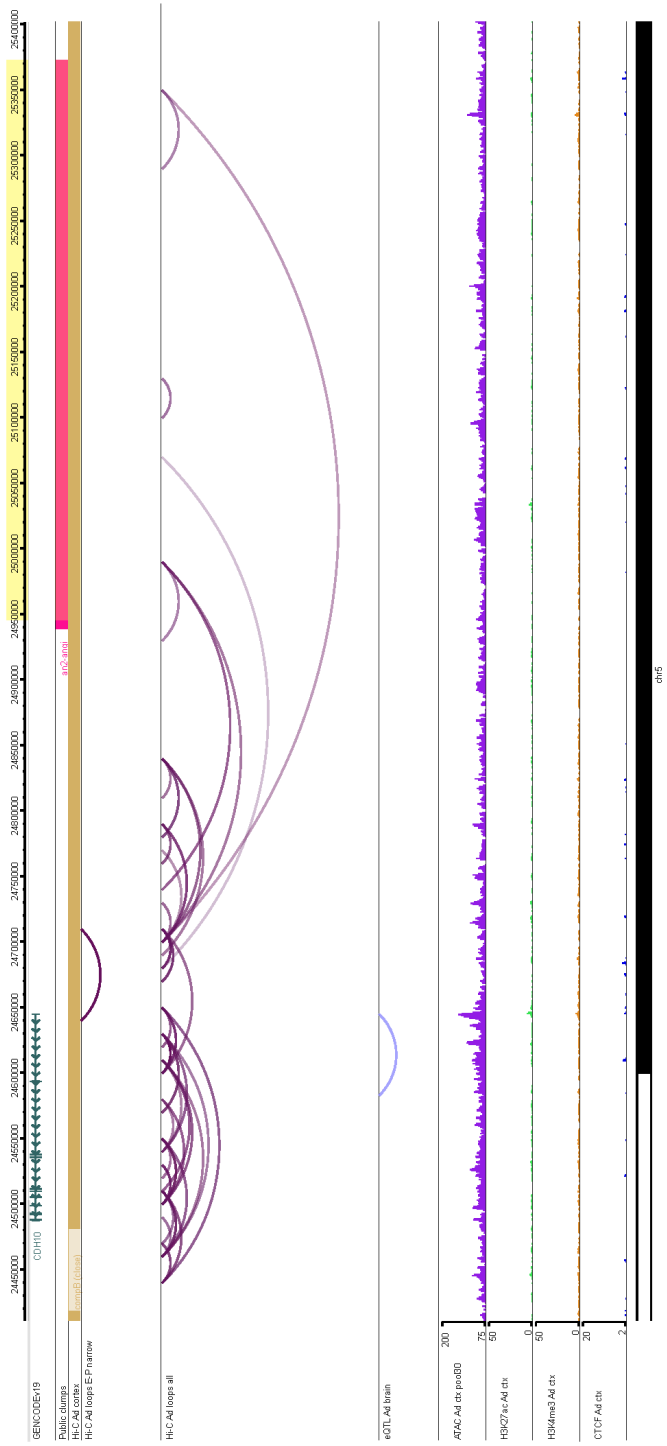
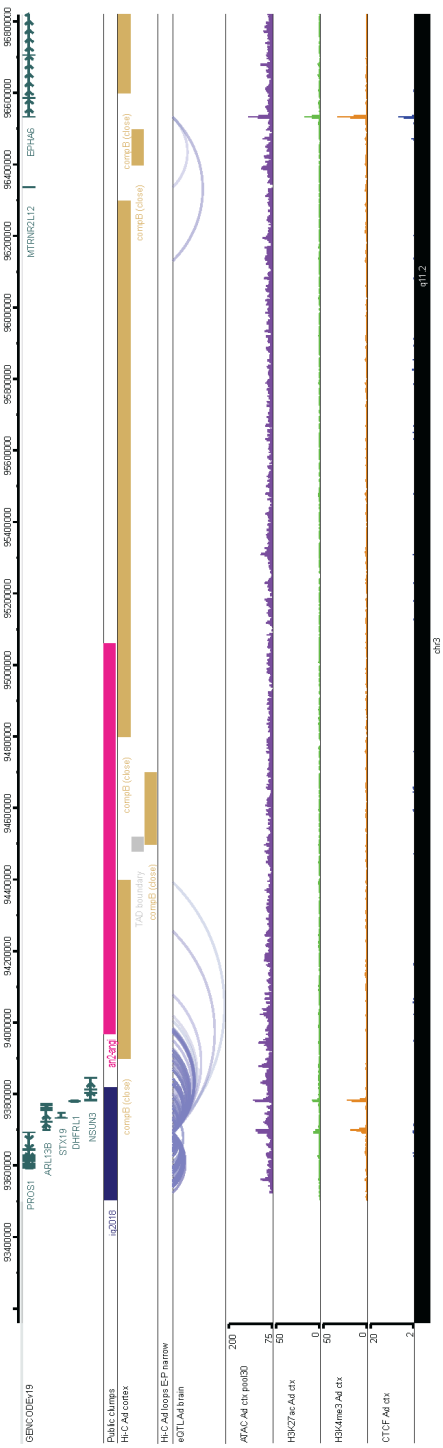
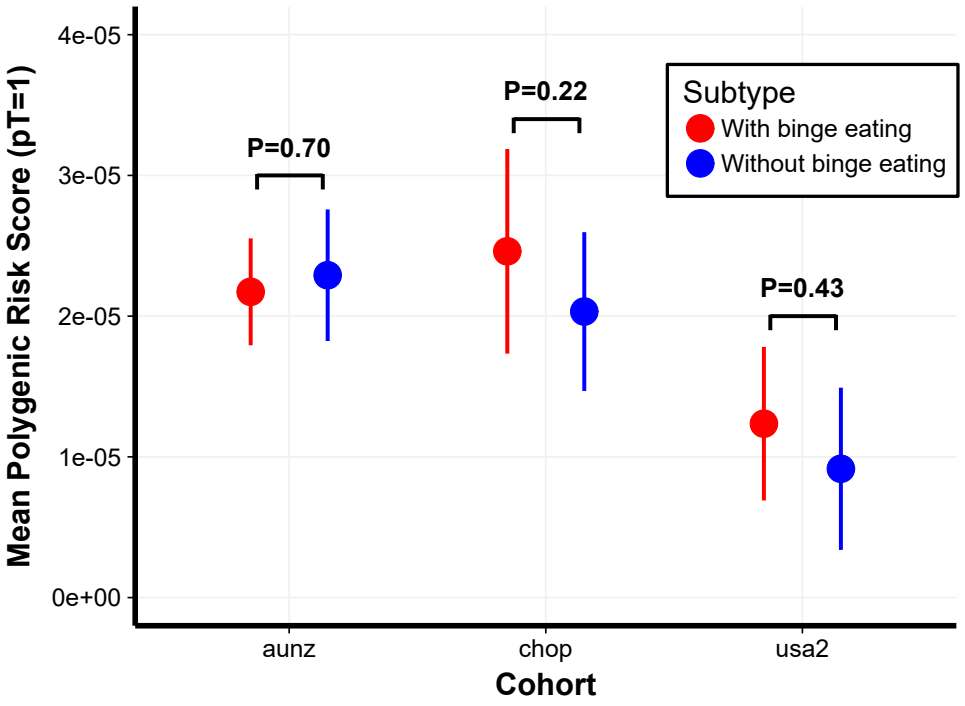


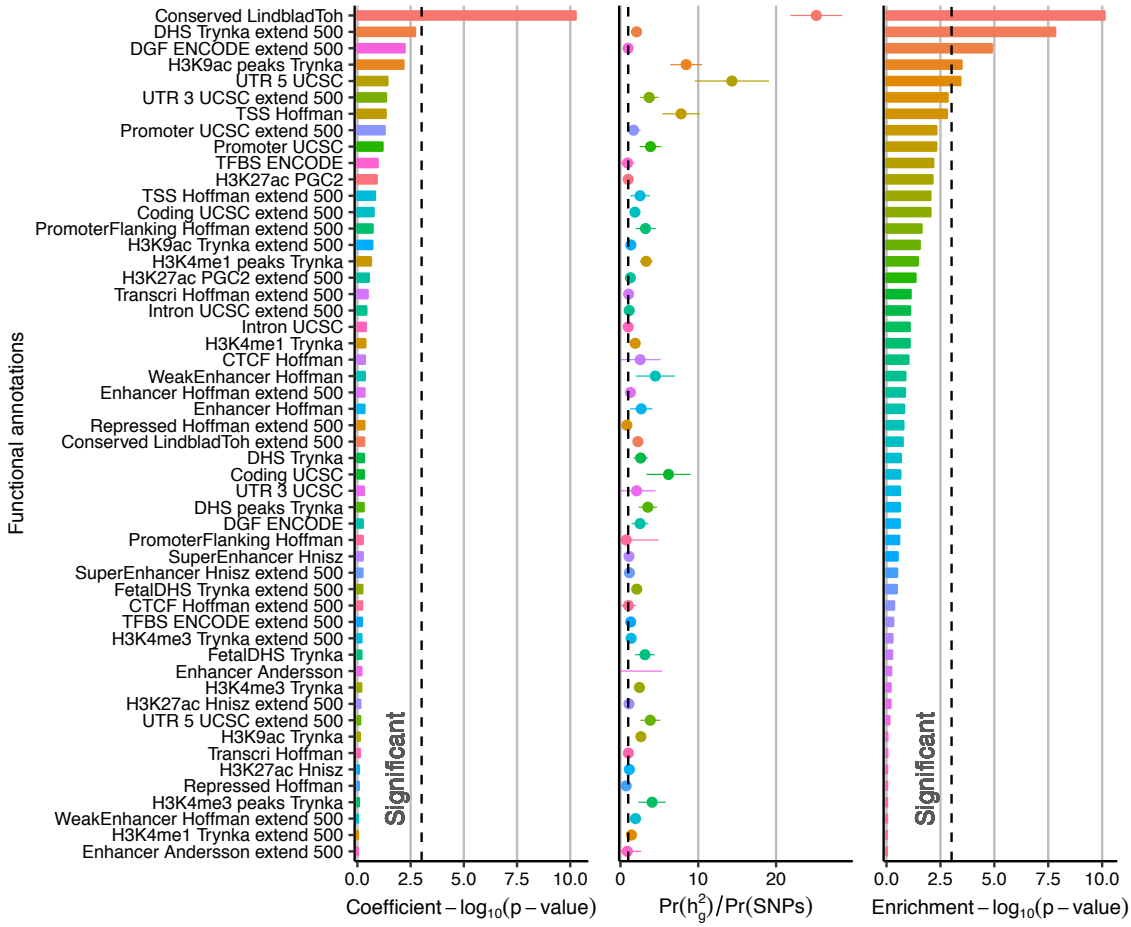
Supplementary Figure 5h



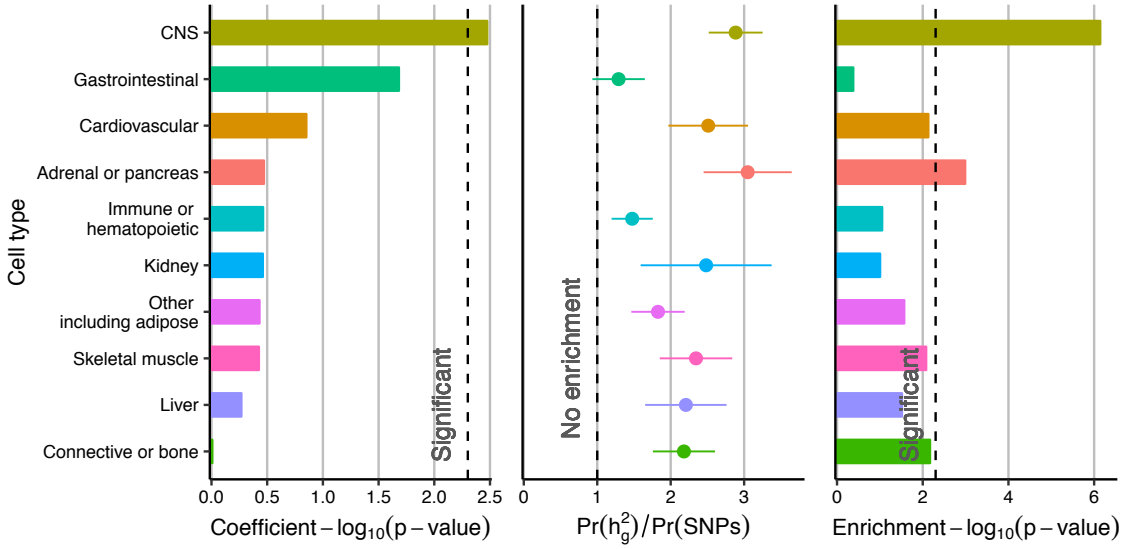
Supplementary Figure 5a-h legend. Hi-C and eQTL analyses. These figures were generated using the WashU EpiGenome browser (http://epigenomegateway.wustl.edu/browser). Yellow shaded regions show the “clumps” associated with AN. The top track shows GENCODE v19 gene models. The "public clumps" track shows psychiatric GWA regions including AN GWAS. The "Hi-C Ad cortex" track shows "compartment A/B", "FIRES" (frequently interacting regions), "superFIRES" (local aggregates of FIREs), and topologically associated domain boundaries (TADs). The "Hi-C Ad loops E-P narrow" contains arcs that show the positions of high confidence chromatin interactions in adult brain (10 Kb resolution) between enhancers and/or promoters (according to ChIP-seq and brain-expressed TSS data) with a Bonferroni $P < 0.001$. The "eQTL Ad brain" track shows cis eQTL information from GTEx for all available brain tissues. The "ATAC Ad ctx pool30" track shows open chromatin data for 30 adult controls. The next three tracks show brain epigenomic marks from ChIP-seq in adult brain cortex (H3K27ac, H3K4me3, and CTCF). We selected eQTL SNP-gene pairs from CommonMind frontal cortex, GTEx in any brain region ($q < 0.05$), or in fetal cortex. Significant eQTL connections were identified by nominal $P < 0.05$ as supplied by CMC and GTEx and significant chromatin interactions were identified with a stringent Bonferroni correction for multiple testing, and only considered 10 Kb bin pairs with P value < 2.31 × 10-11 (0.001/43,222,677 tests). The chromatin interaction tests came from Fit-Hi-C with default parameters applied and FastHiC. All tests were two-tailed.



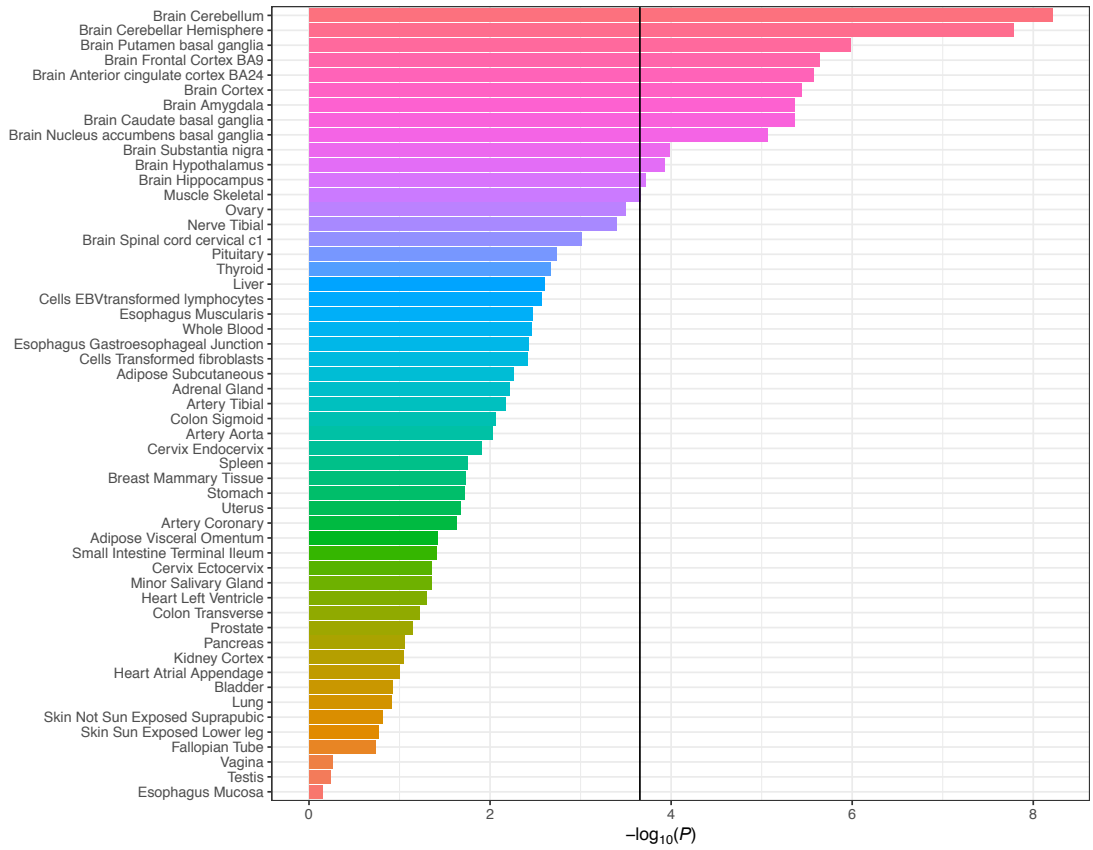
Supplementary Figure 6. Mean polygenic risk scores (PRS) according to anorexia nervosa subtype (+/- binge eating). In the datasets with available subtype data—aunz (1,417 cases with binge eating, 997 cases without binge eating), chop (358 cases with binge eating, 634 cases without binge eating), and usa2 (606 cases with binge eating, 631 cases without binge eating)— AN PRS was computed for each individual. AN PRS was derived from the primary GWAS meta-analysis summary statistics and adjusted for the principal components used in the main GWAS. Individual PRS were then aggregated into subtype group means. The center values show mean PRS and the error bars show the 95% confidence interval. Two-tailed T tests testing for significant differences in PRS scores by subtype were conducted for each cohort using a Bonferroni-corrected P threshold of < 0.017.



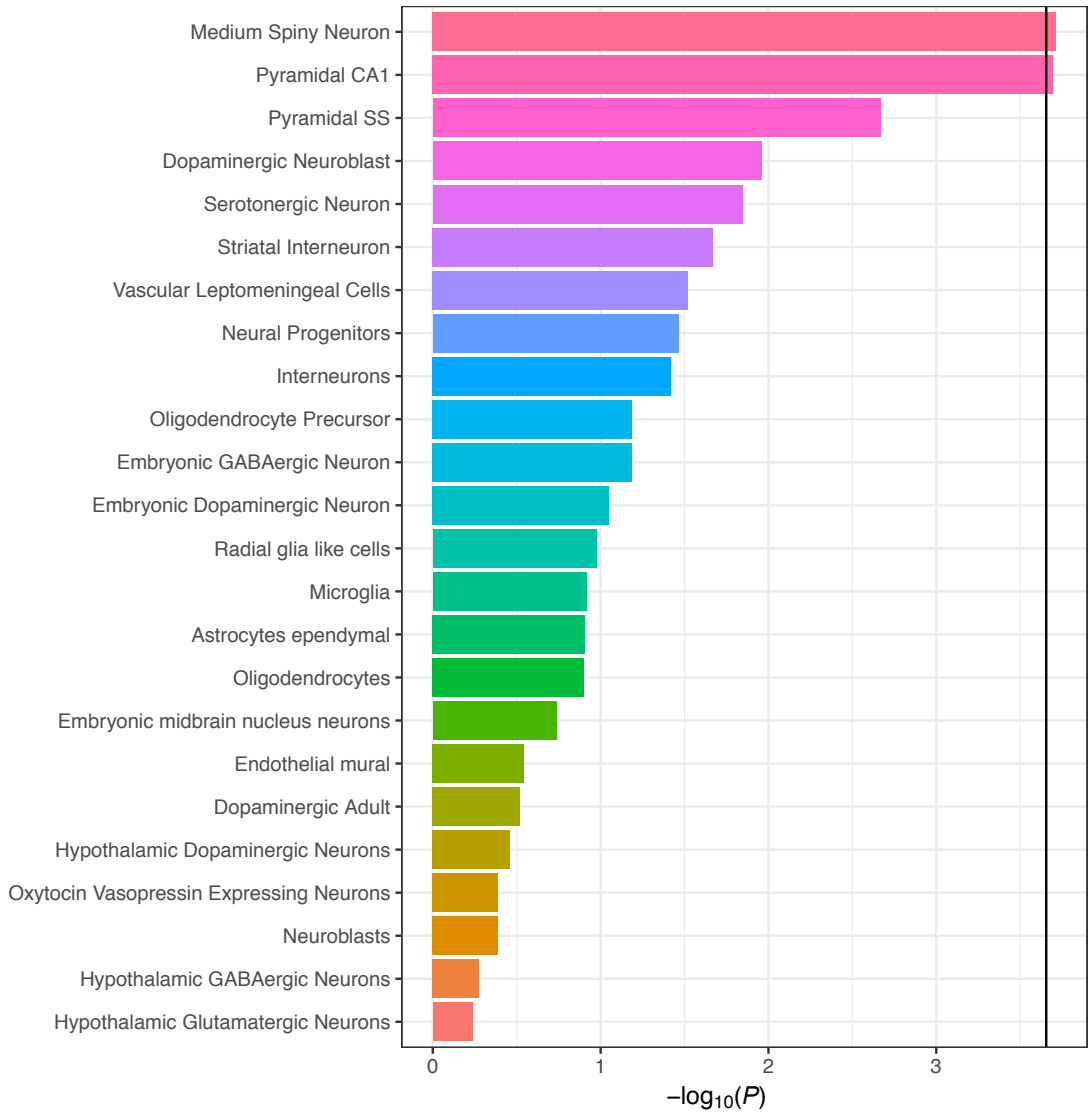
Supplementary Figure 7. Partitioned heritability analysis. The sample size is 16,992 cases and 55,525 controls. The coefficient P value (lefthand) tests for enrichment of heritability within each functional element, controlling for all other functional elements to address overlap. The enrichment P value (righthand) indicates whether this absolute enrichment is statistically significant. In each analysis, the Bonferroni-corrected threshold (vertical line) is -log10(P) > 3.0. The enrichment (middle) scales the heritability captured by each functional element according to the number of variants in the element (vertical line = 1, that is no enrichment). The error bar is the standard error.



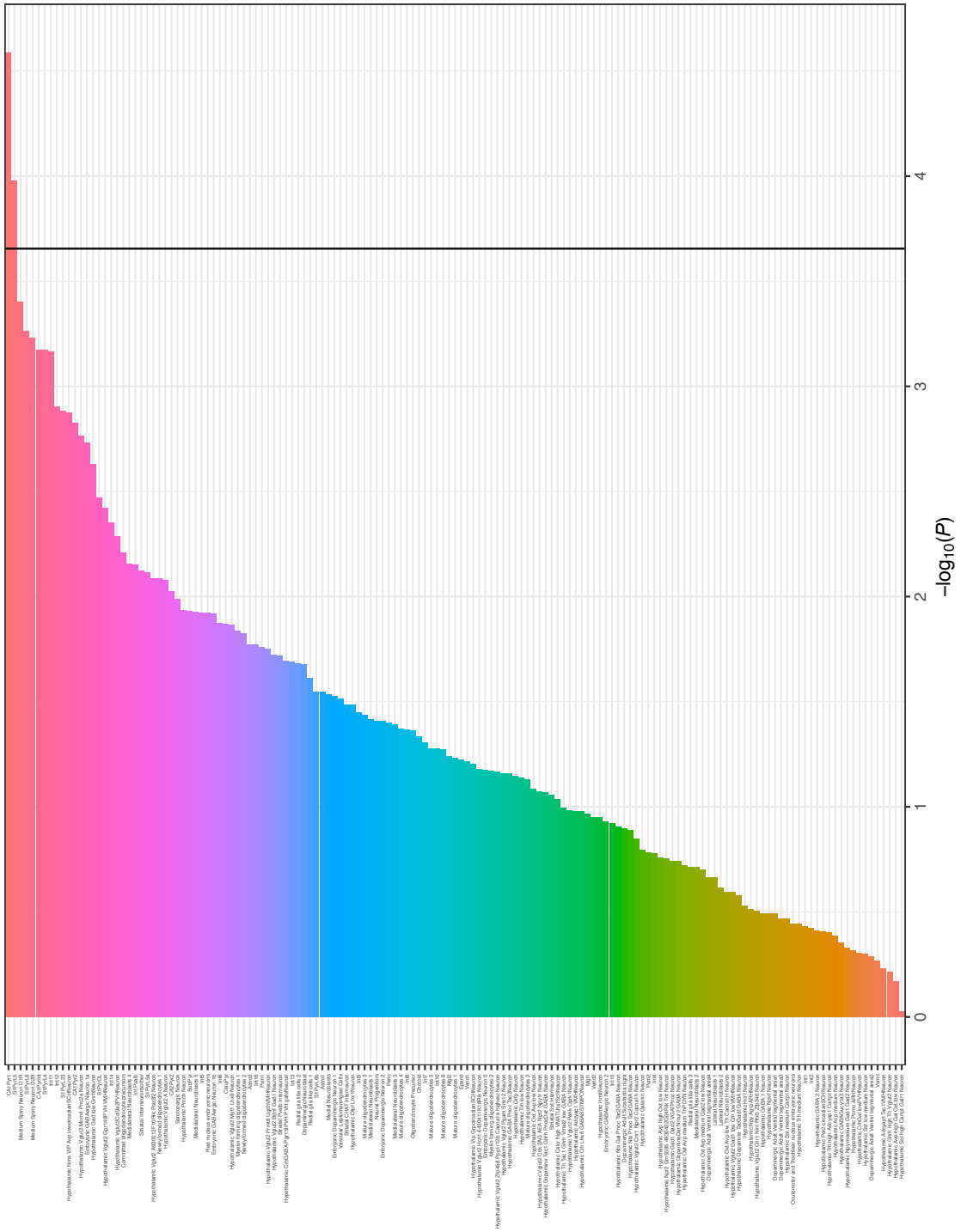
Supplementary Figure 8. Cell type group specific partitioned heritability analysis. The sample size is 16,992 cases and 55,525 controls. The coefficient P value (lefthand) tests for enrichment of heritability within each cell group, controlling for all other cell groups to address overlap. The enrichment P value (righthand) indicates whether this absolute enrichment is statistically significant. In each analysis, the Bonferroni-corrected threshold (vertical line) is -log10(P) > 2.3 (i.e., 0.05/10 tests). The enrichment (middle) scales the heritability captured by each cell group according to the number of variants in the group (vertical line = 1, that is no enrichment). The error bar is the standard error.



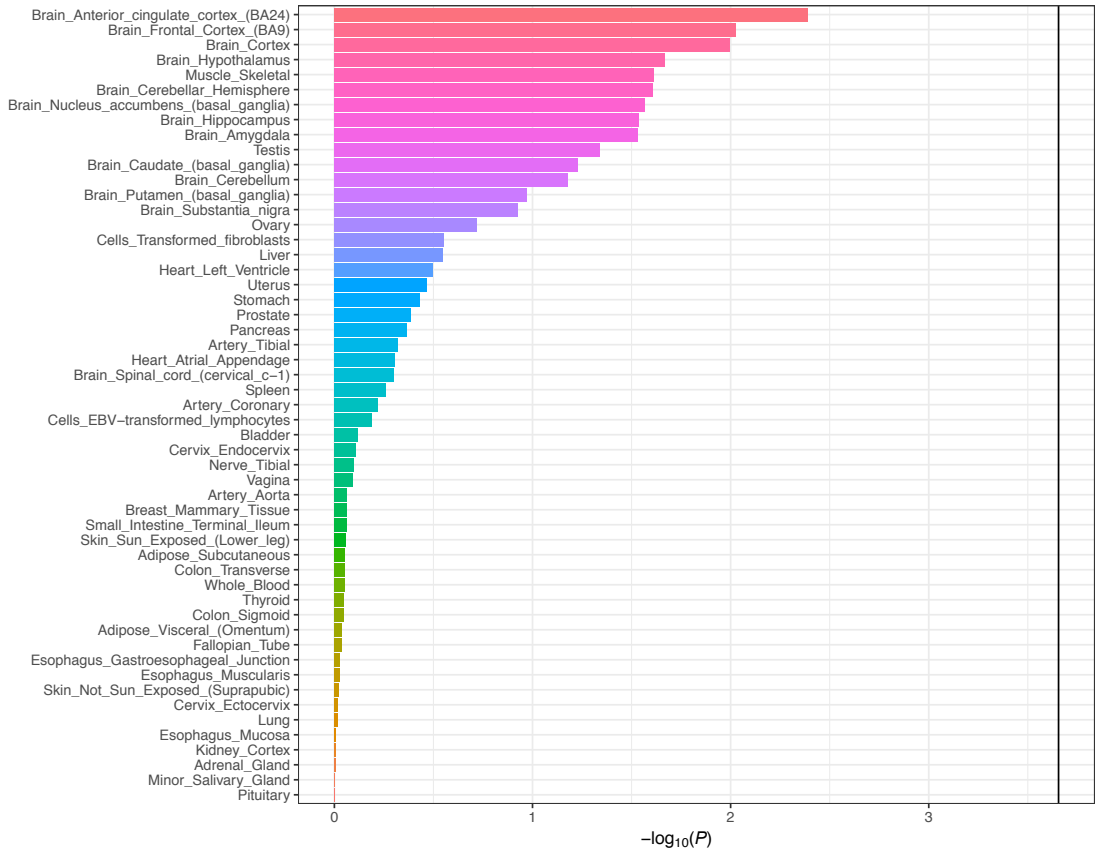
Supplementary Figure 9. P value of association between tissue specificity in GTEx and gene-level genetic association with anorexia nervosa using MAGMA. The sample size is 16,992 cases and 55,525 controls. The Bonferroni-corrected threshold (black vertical line) is -log10(P) > 3.6 and is based on tests across 53 tissues, 24 broad categories of cell types, and 149 KI level 2 cell types, a total of 226 tests.



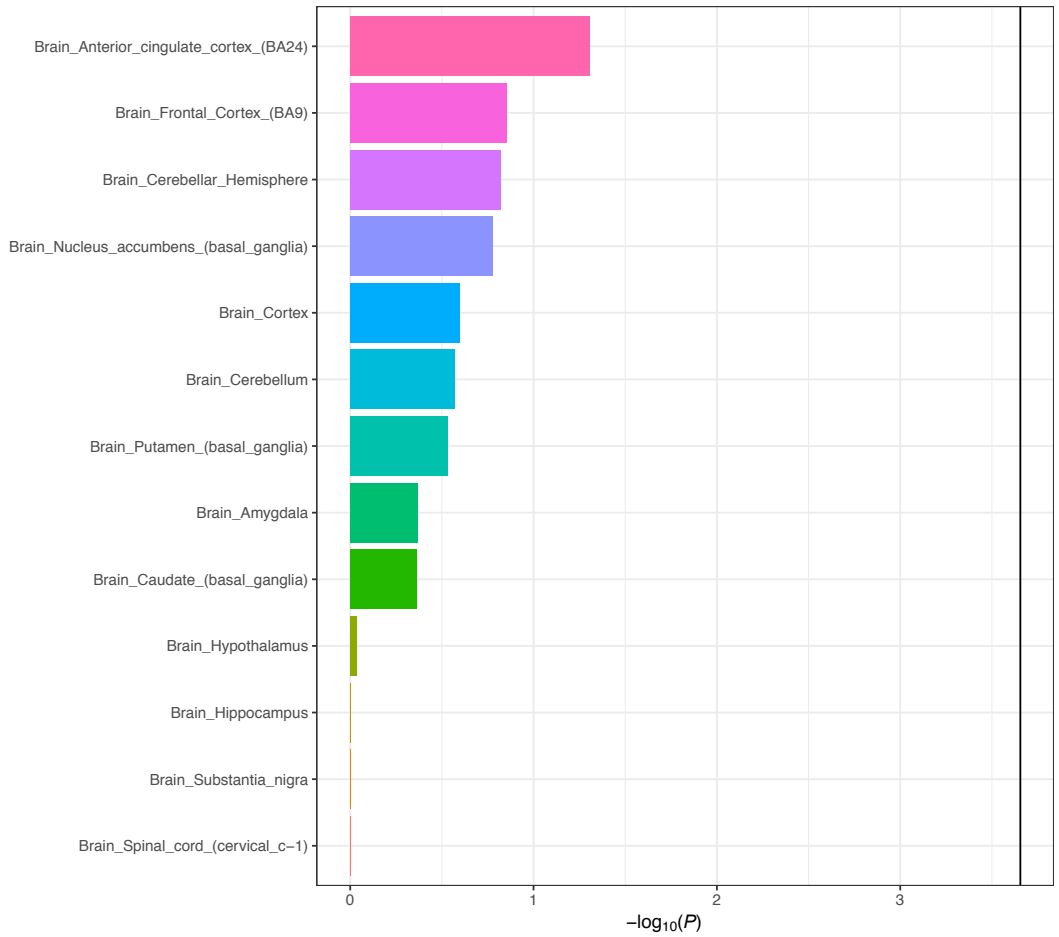
Supplementary Figure 10. P value of association between tissue specificity in 24 brain cell types (level 1) and gene-level genetic association with anorexia nervosa using MAGMA. The sample size is 16,992 cases and 55,525 controls. The Bonferroni-corrected threshold (black vertical line) is $-\log_{10}(P) > 3.6$ and is based on tests across 53 tissues, 24 broad categories of cell types, and 149 KI level 2 cell types, a total of 226 tests.



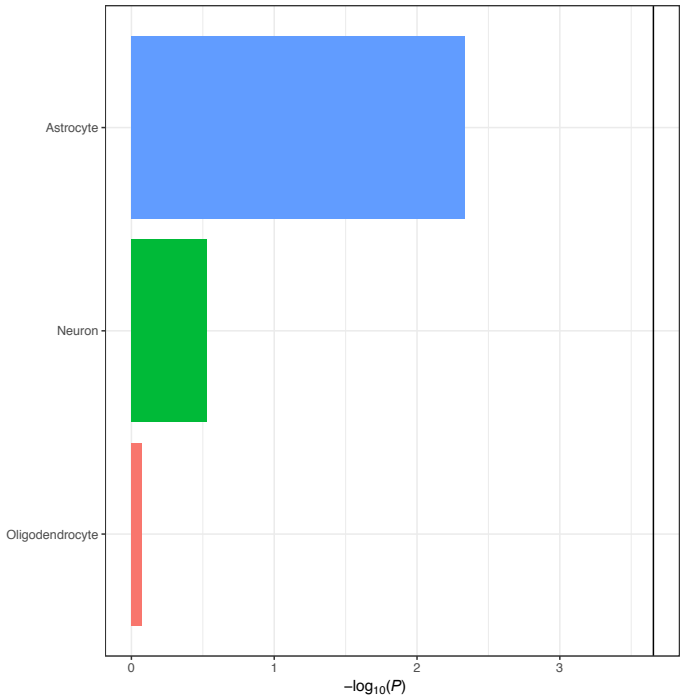
Supplementary Figure 11. P value of association between tissue specificity in 149 brain cell types (level 2) and gene-level genetic association with anorexia nervosa using MAGMA. The sample size is 16,992 cases and 55,525 controls. The Bonferroni-corrected threshold (black vertical line) is -log10(P) > 3.6 and is based on tests across 53 tissues, 24 broad categories of cell types, and 149 KI level 2 cell types, a total of 226 tests.



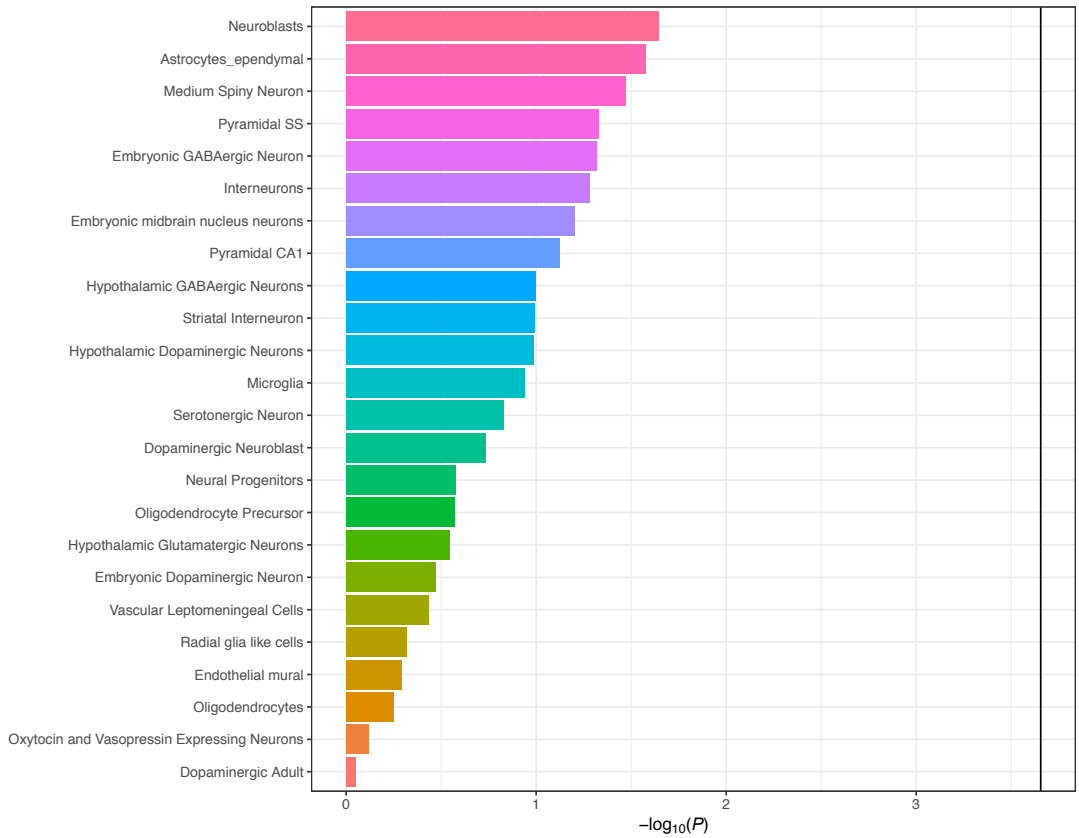
Supplementary Figure 12. P value of enrichment of heritability of anorexia nervosa in each tissue in GTEx using LD score regression applied to specifically expressed genes (LDSC-SEG). The sample size is 16,992 cases and 55,525 controls. The Bonferroni-corrected threshold (black vertical line) is -log10(P) > 3.6 and is based on tests across 53 tissues, 24 broad categories of cell types, and 149 KI level 2 cell types, a total of 226 tests.



Supplementary Figure 13. P value of enrichment of heritability of anorexia nervosa in brain tissues in GTEx using LD score regression applied to specifically expressed genes (LDSC-SEG). The sample size is 16,992 cases and 55,525 controls. The Bonferroni-corrected threshold (black vertical line) is -log10(P) > 3.6 and is based on tests across 53 tissues, 24 broad categories of cell types, and 149 KI level 2 cell types, a total of 226 tests.



Supplementary Figure 14. P value of enrichment of heritability of anorexia nervosa in cell types in Cahoy database using LD score regression applied to specifically expressed genes (LDSC-SEG). The sample size is 16,992 cases and 55,525 controls. The Bonferroni-corrected threshold (black vertical line) is -log10(P) > 3.6 and is based on tests across 53 tissues, 24 broad categories of cell types, and 149 KI level 2 cell types, a total of 226 tests.



Supplementary Figure 15. P value of enrichment of heritability of anorexia nervosa in 24 brain cell types from the single-cell RNA-sequencing database (broad categories) using LD score regression applied to specifically expressed genes
(LDSC-SEG). The sample size is 16,992 cases and 55,525 controls. The Bonferroni-corrected threshold (black vertical line) is -log10(P) > 3.6 and is based on tests across 53 tissues, 24 broad categories of cell types, and 149 KI level 2 cell types, a total of 226 tests.

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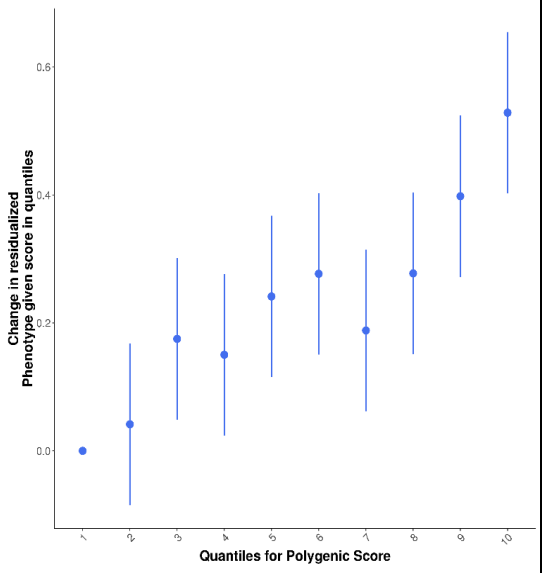

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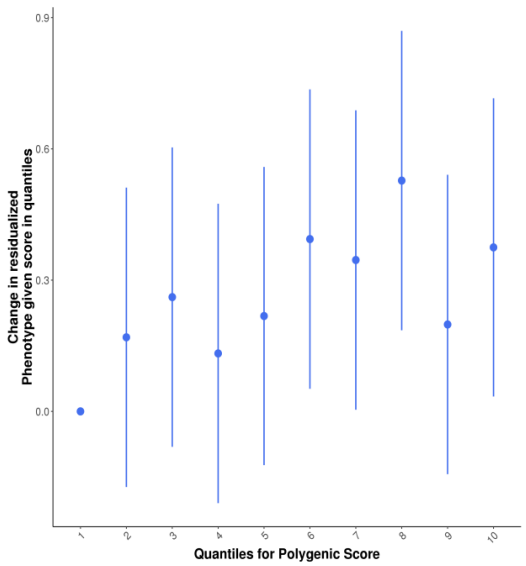

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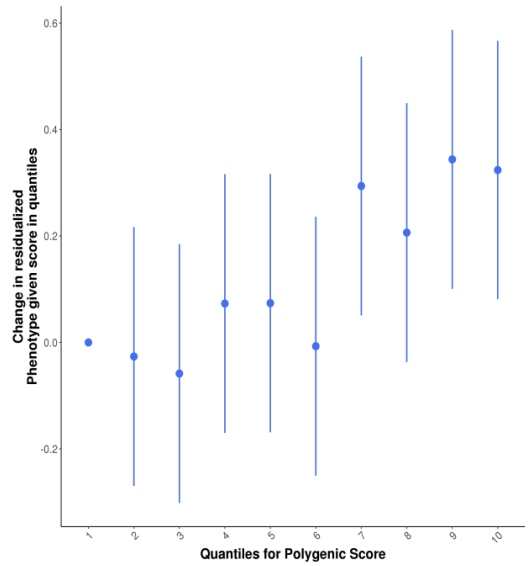

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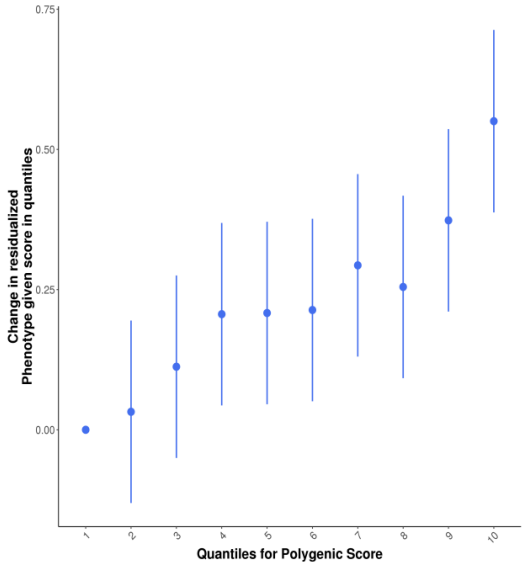

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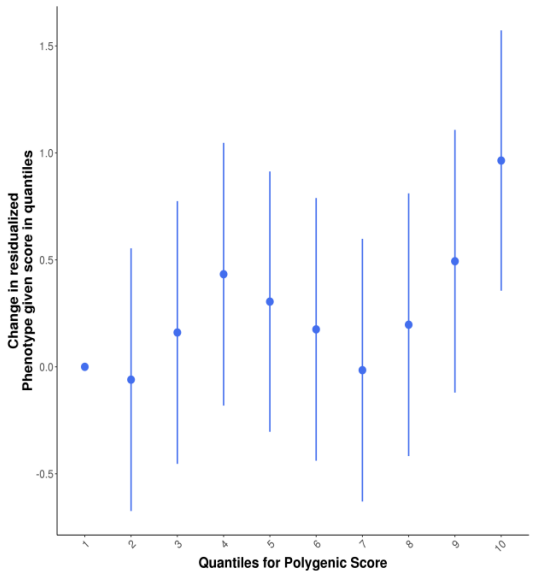

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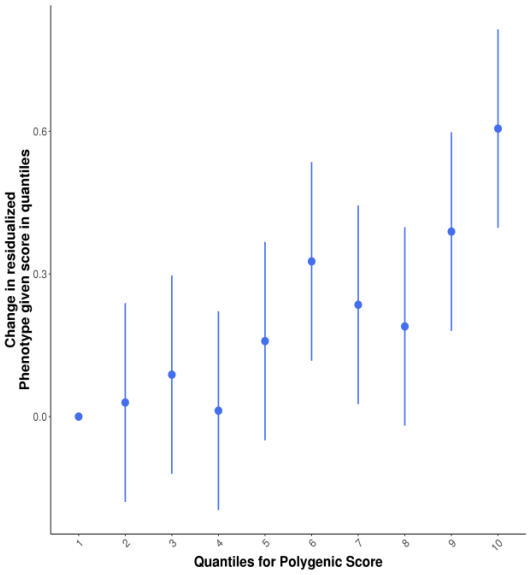

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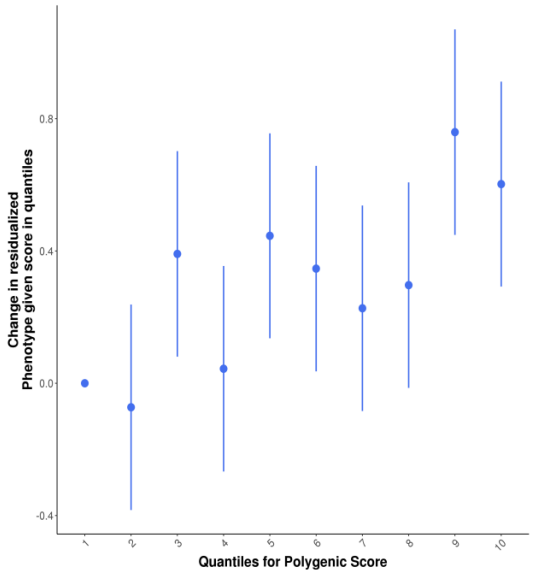

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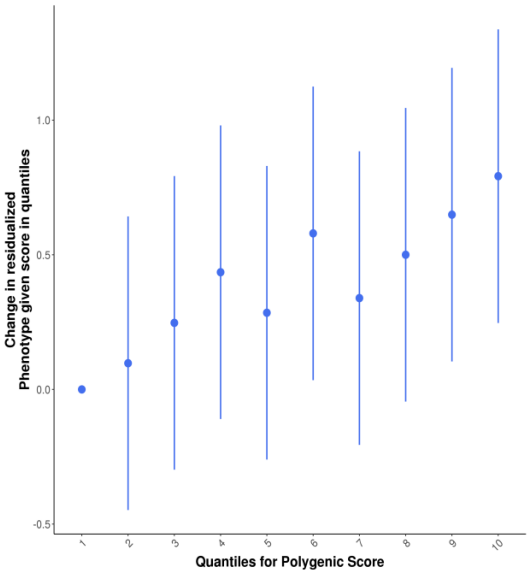

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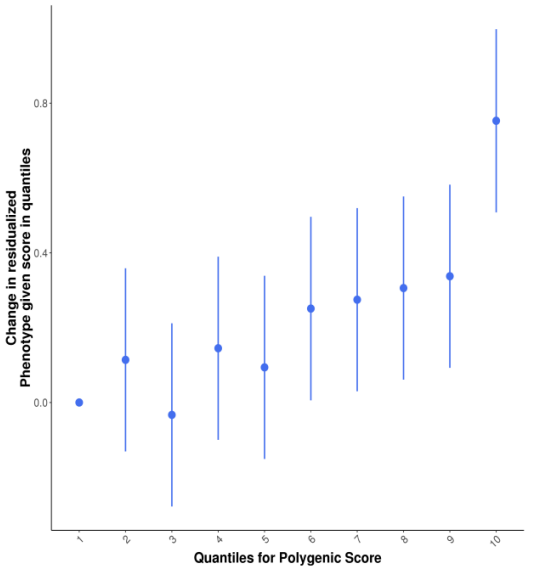

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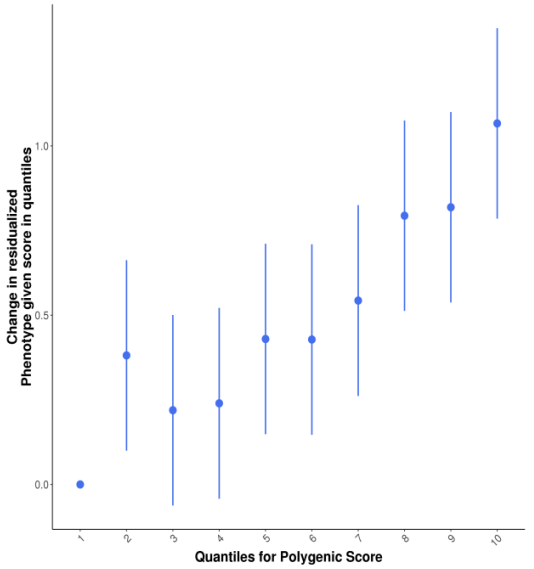

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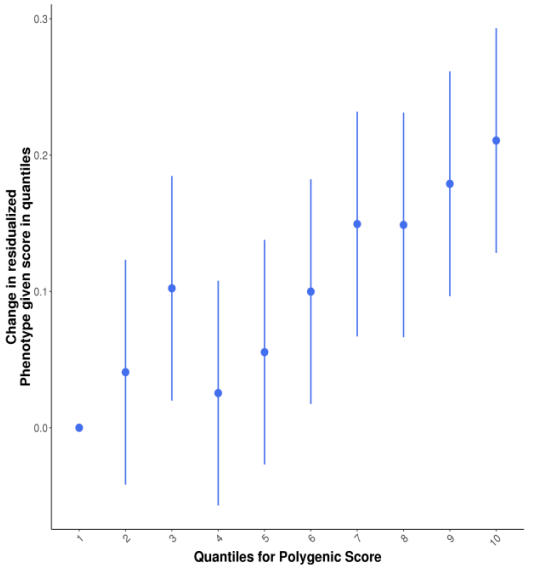

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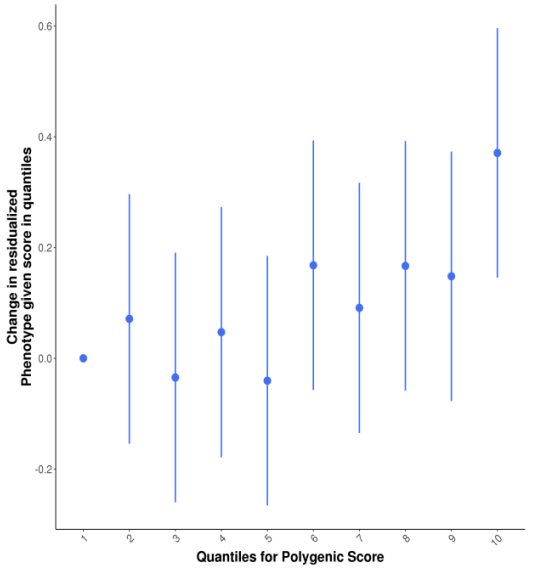

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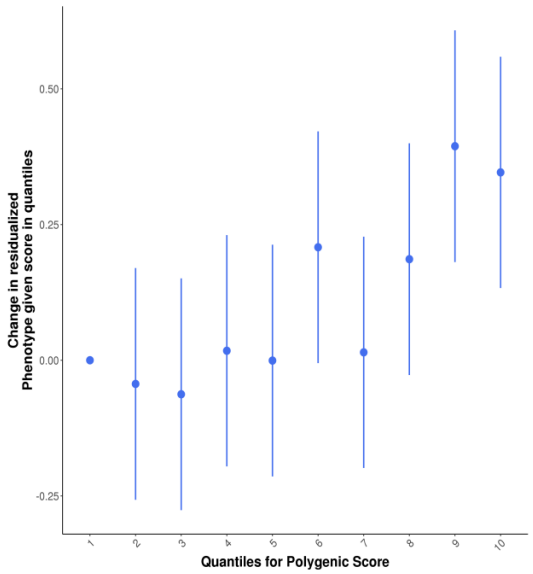

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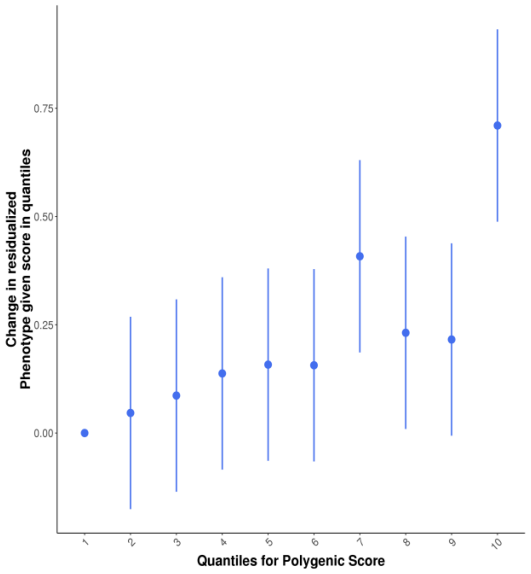

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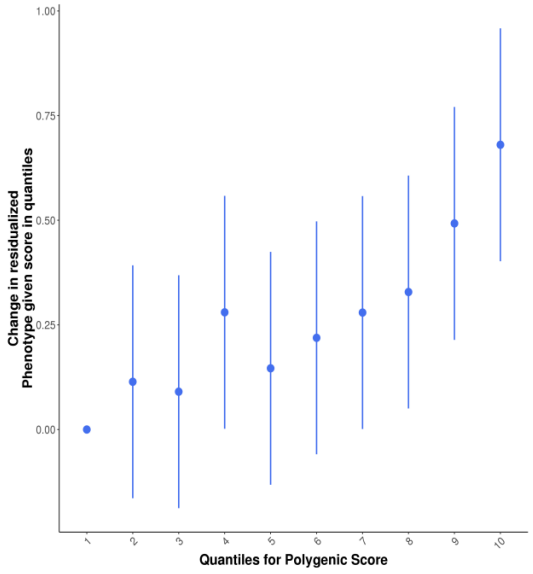

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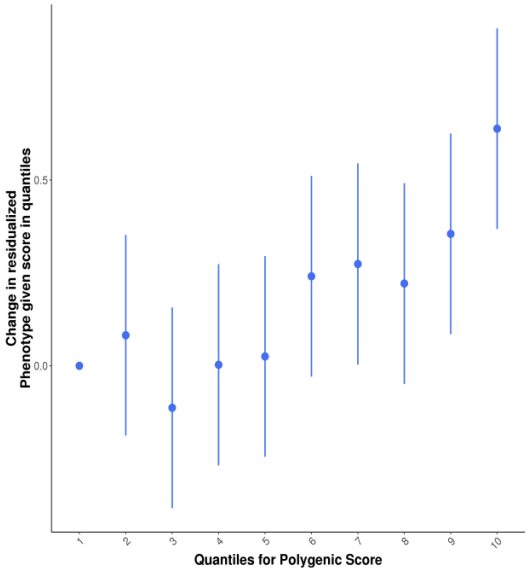

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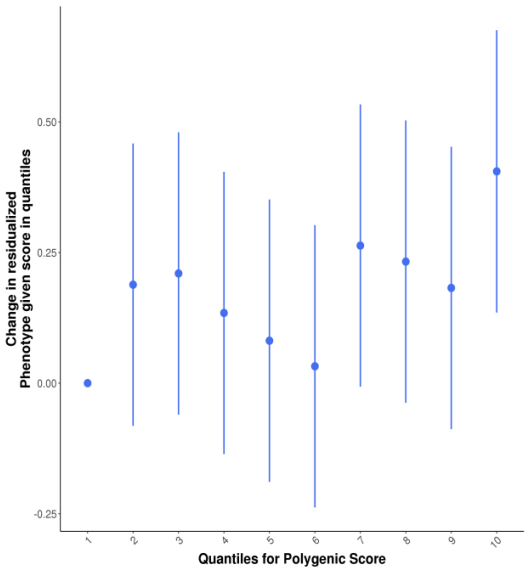

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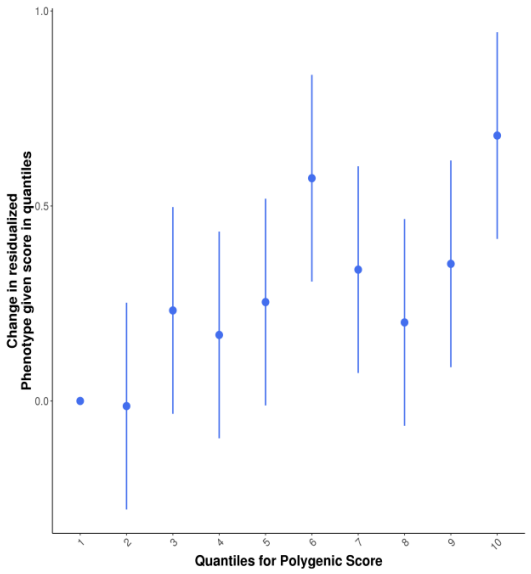

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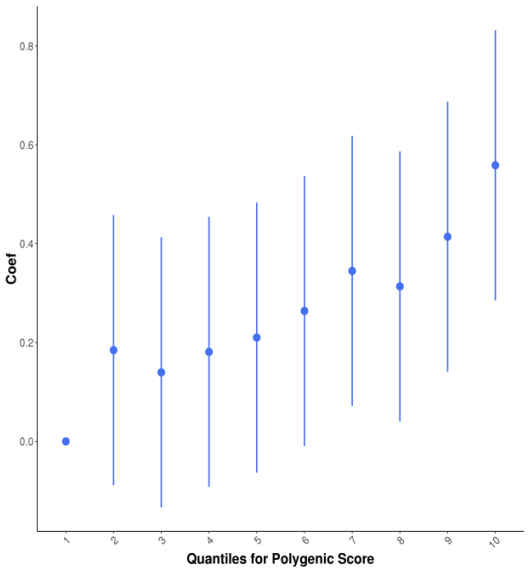

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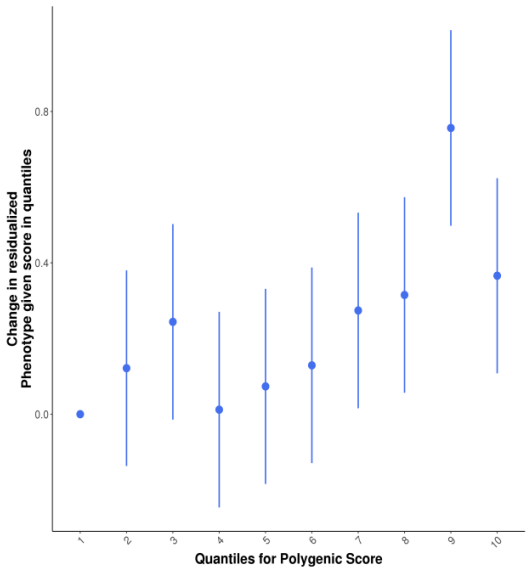

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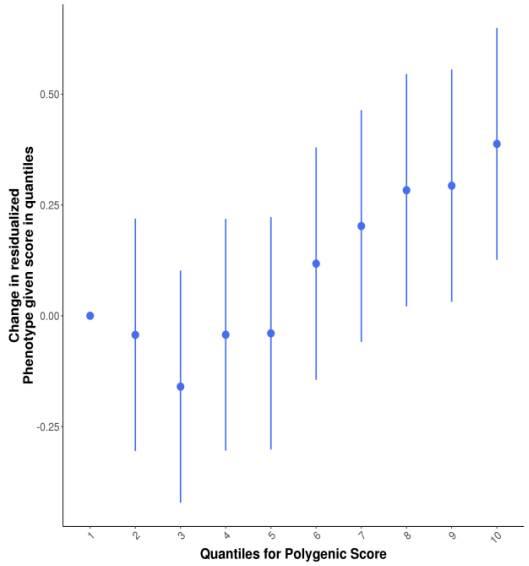

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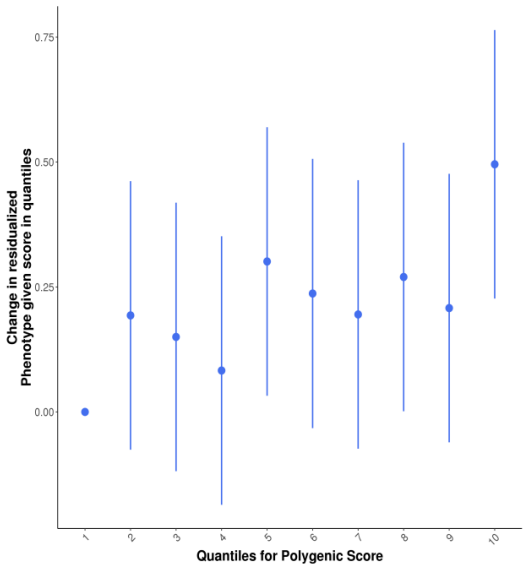

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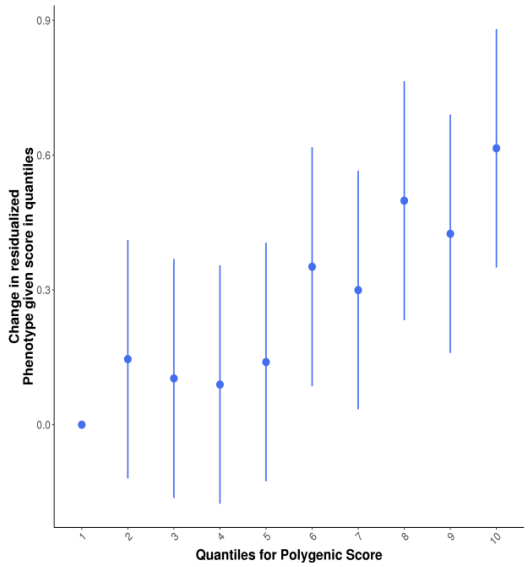

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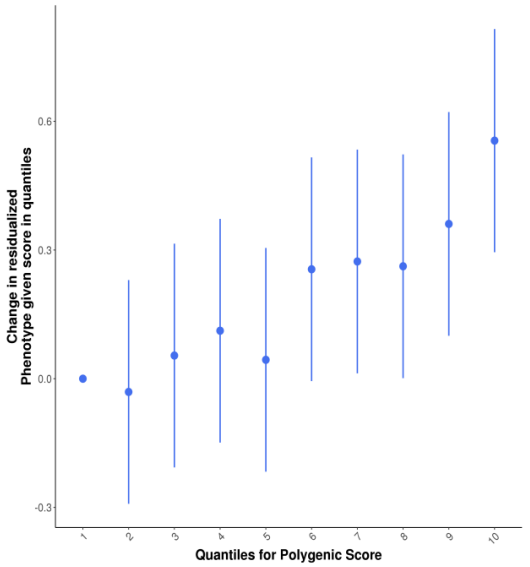

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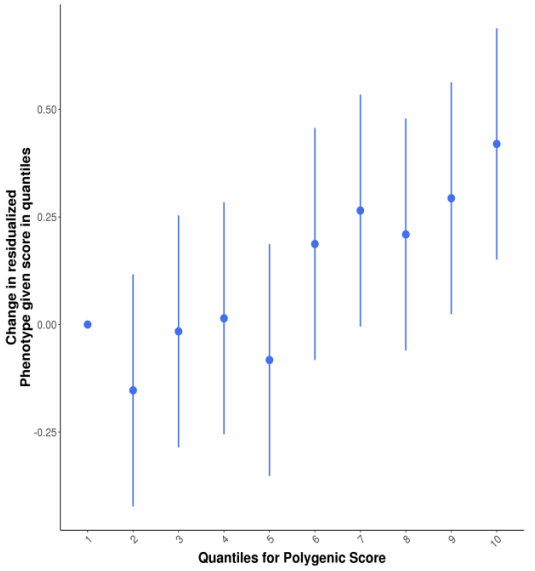

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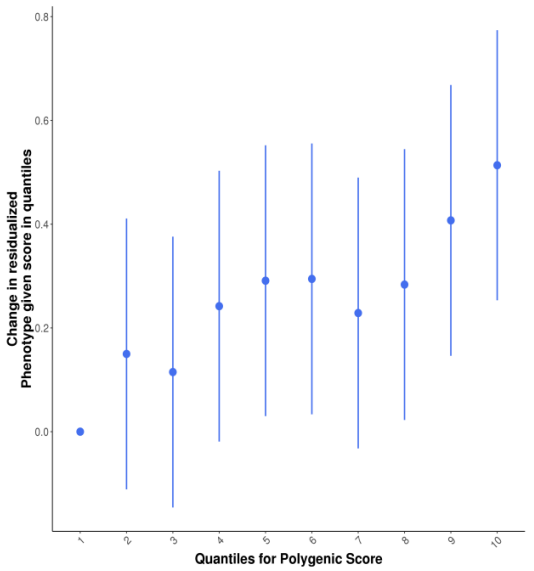

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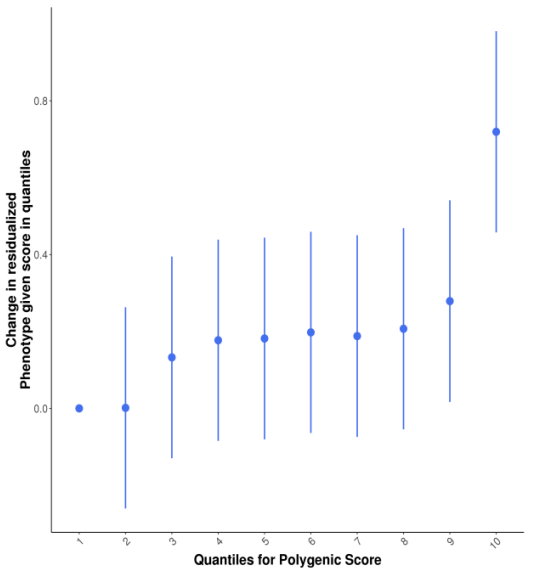

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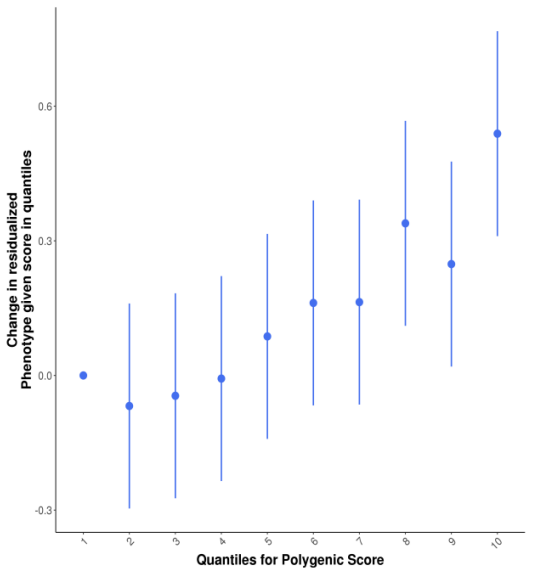

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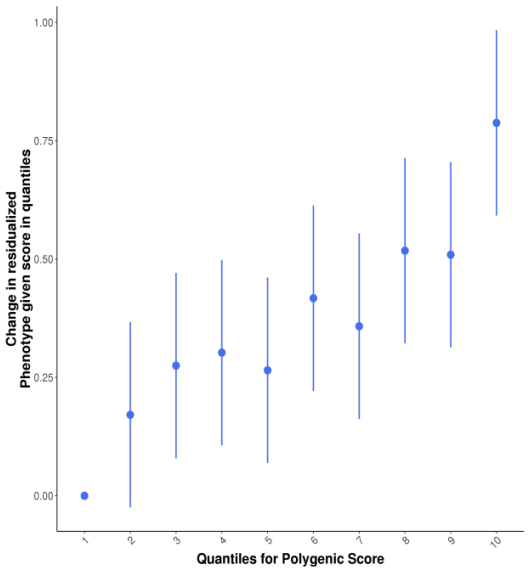

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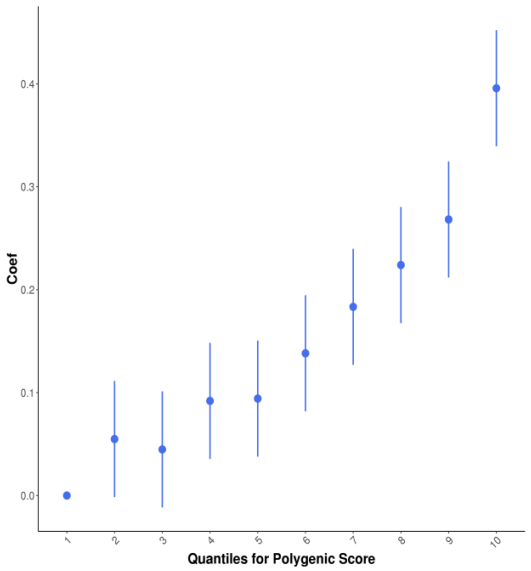

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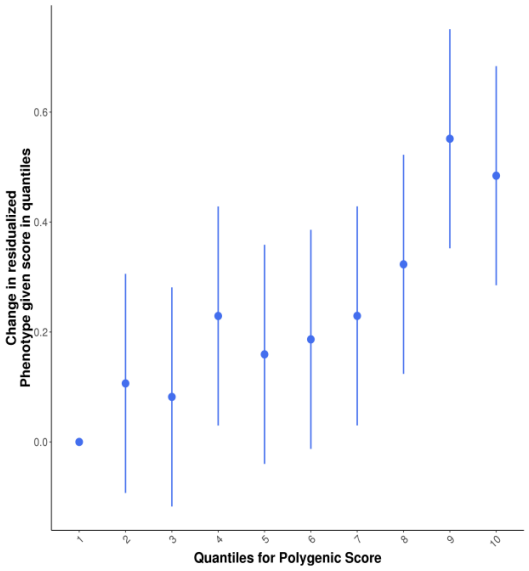

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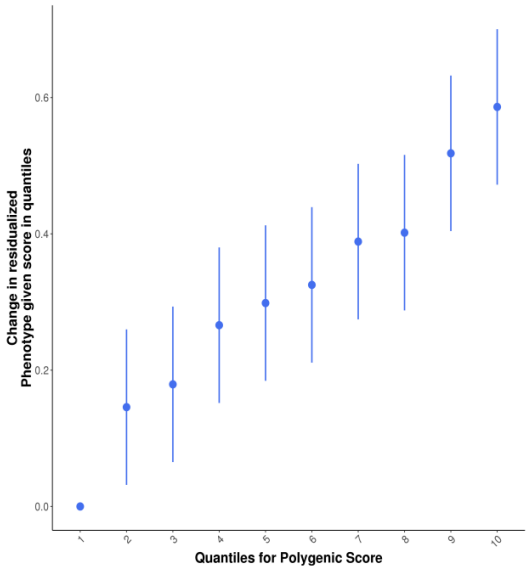

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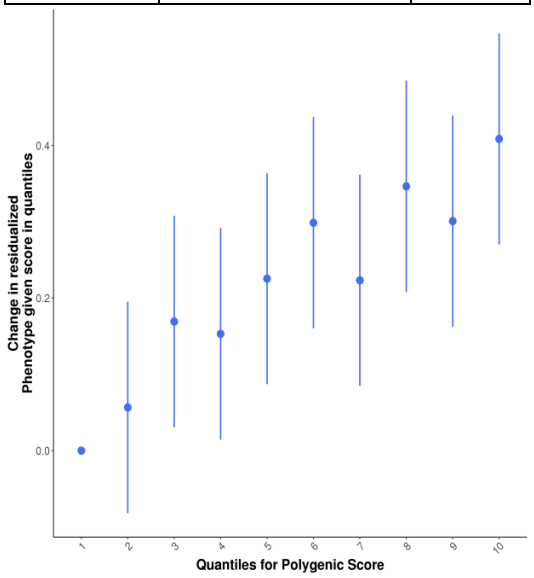

Supplementary Figure 16. Polygenic risk score (PRS) leave-one-out analysis: results for each cohort. PRS was constructed with the leave-one-out method from a GWAS with all datasets excluding the target dataset. Then, PRS was used to predict change in residualized phenotype score for anorexia nervosa (AN) risk in the target dataset (shown as the center value and an error bar which represents the 95% confidence interval of this estimate). The decile with the lowest PRS (i.e., subjects whose AN PRS is in the bottom 10%) serves as the referent. A higher residualized phenotype score indicates a higher risk of AN.

Appendix 4 Genomics of body fat percentage may contribute to sex bias in anorexia nervosa

4.1 Supplementary Methods

4.1.1 UK Biobank

UK Biobank (www.ukbiobank.ac.uk) is a unique epidemiological and prospective resource to generate research findings aimed to improve prevention, diagnosis, and treatment of psychiatric and somatic illnesses. UK Biobank recruited participants from the general population between 2006–2010. All participants were between 40 to 69 years old, were registered with a general practitioner through the United Kingdom's National Health Service, and lived within traveling distance of one of the assessment centres. UK Biobank is approved by The North West Multi-centre Research Ethics Committee. Genomewide array data for this study were available for 488,363 individuals. Due to this trait-specific medication and illness filtering, the final analysis included 155,961 (45% female) healthy and drug-free European participants which are 32% of the genotyped UK Biobank participants (n = 502,682). This study has been completed under UK Biobank approved study application 16577 and 27546.

4.1.2 Body composition

After the removal of shoes and heavy clothing, body weight was assessed using a Tanita BC-418 MA scale (Tanita Corporation, Arlington Height, IL) (http://biobank.ctsu.ox.ac.uk/crystal/docs/Bodycomposition.pdf). Standing height without shoes was assessed with a Seca 202 stadiometer (Seca, Hamburg, Germany). Body mass index (BMI) was calculated by dividing weight in kilograms (kg) by height in metres squared (m^2). Bioelectrical impedance was measured using the Tanita BC-418 MA scale. Participants stood on the footpads of the analyzer in bare feet while holding the handles. This body composition analyzer calculates fat free mass (FFM) and fat mass (FM) from raw bioelectrical impedance data, using standard formulas including sex, age, height, and athletic or normal mode. We excluded people whose hydration status might be compromised such as by reported alcohol use disorder, metabolic diseases, or by medication (Supplementary Table S1). Bioelectrical impedance analysis (BIA) technology has been extensively validated (Genton et al., 2003; Kyle et al., 2004). Assessing body fat percentage (BF%) by BIA results in more reliable estimates than body mass index (BMI) for healthy individuals (Mazzoccoli, 2016; Tanamas et al., 2016), is the most feasible in large epidemiological samples, and does not expose participants to radiation.

4.1.3 Descriptive statistics and phenotypic associations

In our descriptive analyses, we choose to report means and standard deviations (SD) for continuous variables and frequencies and percentages for categorical variables. We used the Pearson product moment correlation coefficient to describe associations. We stratified by sex to calculate male- and female-specific genome-wide association studies (GWAS). Analyses were conducted in R version 3.3.2, if not otherwise specified.

4.1.4 Residualisation of the phenotype

We residualized the outcome variables BF% and FFM by performing a multiple regression in R. We included factors related to assessment centre, genotyping batch, smoking status, alcohol consumption, menopause, and continuous measures of age, and socioeconomic status (SES) measured by the Townsend Deprivation Index as independent variables. The Townsend Deprivation Index indicates the level of social deprivation in an area (Townsend, 1987). A higher score indicates a lower average SES. We accounted for underlying population stratification by including the first six ancestry principal components, calculated from genome-wide data on the European subsample using FlashPCA2 (Abraham, Qiu, & Inouye, 2017), in the regression.

4.1.5 Power calculations of the genome-wide association studies

We conducted power calculations for the female and male GWAS using the Genetic Power Calculator (Purcell, Cherny, & Sham, 2003). Power of 80% at a genome-wide significance threshold of $p \leq 5x10^{-8}$ and a MAF 0.20 to detect a SNP that accounts for 0.1% of trait variance requires 39,580 individuals. According to these results the female and the male GWAS were sufficiently powered to detect genome-wide significant loci with 70,700 females and 85.261 males. With these parameters, the female GWAS had a power of 99.8% and the male GWAS of 99.9%.

4.1.6 Genotyping, imputation and quality control

Blood samples were genotyped on two arrays, which share nearly all of their content: the UKBileve array (N = 49,949) or the UK Biobank Axiom array (N = 438,414). Genotyping was conducted by Affymetrix and was distributed across 33 different batches of approximately 4,700 samples. UK Biobank provides extensive information on sample processing on its web site, http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155583, and details of the Axiom array are available at http://media.affymetrix.com/support/downloads/manuals/axiom_2_assay_auto_workflow_user_guide.pdf. UK Biobank performed stringent quality control on the genotyping data at the Wellcome Trust Centre for Human Genetics (WTCHG). For further details, see: http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155580. Prior to imputation, all variant sites with a call rate below 90% were filtered out. Imputation was carried out by UK Biobank using the IMPUTE3 program and a

merged UK10K-1000 Genomes Phase 3 reference panel (details available at http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=157020).

We applied additional quality controls. Specifically, we excluded genotyped participants who were pregnant (N = 105), had a International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (World Health Organization, 1992) psychiatric disorder diagnosis described in chapter V (F00–F99) (N = 32,510), or self-reported a psychiatric disorder in the mental health questionnaire (N = 40,435), or a somatic disease influencing body composition (N = 130,663), or were taking medication (N = 108,314) that could influence body composition (Supplementary Table S1). Medications were classified using Monthly Index of Medical Specialities (MIMS), British National Formulary (BNF), DrugBank, and Martindale. These numbers do not sum up to the total number excluded as participants could suffer from multiple diseases or were taking multiple medications. Furthermore, we excluded non-European participants identified by k-means clustering (k = 4) on the first two principal components derived from the genotype data, and we excluded related individuals (KING relatedness metric >0.088, equivalent to a relatedness value of 0.25; N = 7,765) Only participants with complete data were analyzed (N = 155,961). SNPs were excluded if they had a minor allele frequency (MAF) smaller than 1%, if no call was made in more than 2% of samples following imputation, if they were imputed with low confidence (INFO<0.8), if they deviated substantially from Hardy-Weinberg equilibrium (HWE test, $p<10^{-7}$), or if they were not genotyped and not part of the HRC reference panel (McCarthy et al., 2016). This left a total of 7,794,483 SNPs for analysis.

4.1.7 Genome-wide association studies on body composition measures in UK Biobank

We calculated sex-specific GWAS on the residualised BF% and FFM, using the program BGENIE v1.2 with the imputed genotype data supplied by UK Biobank (software available at https://jmarchini.org/bgenie/) (Bycroft et al., 2017). An additive model was used. Furthermore we used the current version of METAL (http://csg.sph.umich.edu/abecasis/metal/) to meta-analyze applying a variance-weighted fixed-effect statistical method those sex-specific GWAS (Willer, Li, & Abecasis, 2010). Independent loci were estimated by linkage disequilibrium (LD) clumping in Functional Mapping and Annotation (FUMA; Watanabe, Taskesen, van Bochoven, & Posthuma, 2017). This reflects the degree to which genome-wide significant hits tag independent regions and/or haplotypes as defined by the LD structure of the data. The most strongly associated SNPs (with a p value of < $5x10^{-8}$) were considered as potential index SNPs. SNPs in LD (r^2 > 0.2) with a more strongly associated SNP within 3000kb were assigned to the same locus using Functional Mapping and Annotation (FUMA; Watanabe et al., 2017). Overlapping clumps additionally were merged with a second clumping procedure in FUMA

merging all lead SNPs with $r^2 = 1$ to genomic risk loci. After clumping, independent genome-wide significant loci ($5x10^{-8}$) were compared with entries in the NHGRI-EBI GWAS catalog using FUMA (MacArthur et al., 2017).

4.1.8 Genome-wide association study on neuroticism in UK Biobank

We calculated sex-specific GWASs on neuroticism using the genotype data (prior to imputation) supplied by UK Biobank in males (N = 142,875) and in females (N=144,660; total N = 287,535), following QC as described above. The neuroticism phenotype was calculated as the sum score of neuroticism questions at the baseline assessment (Smith et al., 2013), corrected for age and sex-specific means and standard deviations from the UK population (Eysenck, Eysenck, & Barrett, 1985). In a second analysis, individuals were excluded if they reported any psychiatric illness, resulting in 83,413 males and 73,946 females (total N = 157,355; Supplementary Table S1). Sex-stratified linear regressions were performed in PLINK using eight genomic principal components and genotyping batch (as a factor) as covariates and later meta-analyzed using METAL (Willer et al., 2010).

4.1.9 Genome-wide association study on physical activity in the UK Biobank

We calculated sex-specific genome-wide association analyses of physical activity with imputed genotype data in 29,496 male and 36,758 female (N = 66,254) individuals in the UK Biobank, including age (at recruitment), genotyping array, and genetic principal components 1–20 as covariates. Physical activity in the UK Biobank was measured continuously over a period of 7 days with a wrist-worn accelerometer. General physical activity quality control of raw data is described in detail elsewhere (Doherty et al., 2017). We used a wear-time adjusted 7-day average measure of activity, including only individuals meeting UKB QC criterion: good wear-time, good calibration, calibration on own data, and no problem indicators. Our analyses were performed on the intersection of this UK Biobank subset with those passing general genotyping QC: in white British ancestry subset, used in the calculation of ancestry principal components, without excess relatives in the UK Biobank sample, no putative sex chromosome aneuploidy, and were not outliers for heterozygosity and genotype missingness. General genotyping considerations, raw data QC, and imputation procedure in the UK Biobank are described in detail elsewhere (Bycroft et al., 2017).

4.1.10 Genome-wide association study on anxiety in the UK Biobank

We calculated genome-wide association analyses of anxiety disorders with imputed genotype data on 25,443 cases compared to 58,113 controls (Purves et al., 2017). Cases met criteria for probable lifetime anxiety disorder diagnosis if they either self-reported a professional diagnosis of any of the five core anxiety disorders (generalized anxiety disorder, panic disorder, specific phobia, agoraphobia, or social anxiety disorder) or met criteria for probable lifetime

generalized anxiety disorder according to the Composite International Diagnostic Interview question set (Davis et al., 2018; Kessler, Andrews, Mroczek, Ustun, & Wittchen, 1998). Cases did not report a diagnosis of schizophrenia, psychosis, ADHD, autism, any eating disorder, or bipolar disorder. Controls were screened for any evidence of psychiatric or substance use disorders. Participants were limited to individuals of white European ancestry, who were not excessively related, had no putative sex chromosome aneuploidy, and were not outliers for heterozygosity and genotype missingness. Stratified linear regressions were performed on ~7 million SNPs of high imputation quality (INFO > 0.9) with a minimum minor allele frequency of 1% in BGENIE v1.2 controlling for six genetic principal components, assessment center, genotyping batch, and age.

4.1.11 Genetic correlations

Using an analytic extension of LDSC, we calculated genetic correlations (*SNP-*r_g) across the computed GWAS and with a wide range of metabolic measures, such as body composition, insulin sensitivity, fasting glucose and insulin, physical activity, and psychiatric traits and disorders, such as depression and neuroticism. For some of these traits, sex-specific summary statistics were available. *SNP-*r_g capture the degree to which traits or disorders share common genetic variants and here are estimated using the pattern of LD across the genome. The contribution of any SNP to the phenotype comprises both its own contribution, and the contribution of all variants with which it is in LD. SNPs in regions of high LD are thus more likely to be in LD with a variant that has a true effect on the trait of interest. SNPs in higher LD, therefore, represent a greater proportion of variance in the phenotype on average, than SNPs in regions of lower LD. The *SNP-*r_g were corrected for multiple comparisons after assessing the number of independent tests by matrix decomposition. Furthermore, we tested whether the *SNP-*r_g between the females and males GWAS were significantly different from 1 calculating a standard error using a block jackknife method (Bulik-Sullivan, Finucane, et al., 2015; H. Finucane, personal communication, 2017).

4.1.12 Matrix decomposition to identify number of independent tests

We used a Bonferroni threshold (by correcting α as α/N) to estimate the number of significant genetic correlations, with N = estimated number of independent tests. We built a similarity matrix reflecting the trait similarity where D = number of principal components accounting for 99.5% of the data variance in the genetic correlation matrix. In that case, D is the estimated number of independent traits (GWAS), and the number of independent tests can be computed as $N = (D(D\text{-}1))/2$.

4.1.13 Sex-specific analyses of genetic determinants of body composition

We investigated differences between females and males in heritability, *SNP-*h^2, and genetic architecture, *SNP-*r_g. We calculated differences (d) in the *SNP-*h^2 estimates between males and females and their standard errors. We calculated the *SNP-*r_g of

female and male GWASs, and tested whether this was different from 1 to identify potential genetic heterogeneity between the sexes using the same approach. We calculated the *SNP-*r_g of the female and male GWAS with AN separately to investigate the relationship of the heterogeneity with the risk for AN. To test the statistical significance of all estimates, we calculated their standard error and corresponding *p* value by applying a block jackknife method, as described and implemented in ldsc v1.0.0 by Bulik-Sullivan et al. (2015).

4.1.14 Block jackknife method

Comparing two genetic correlations using jackknife and ldsc

Let there be four phenotypes A, B, C, and D. The goal is to compare the genetic correlation between A and B to the genetic correlation between C and D. Global estimates of these correlations can be computed using the ldsc software and will be noted r(A,B) and r(C,D). The same software can output jackknife delete values for genetic covariance: G(A,B), G(C,D), as well as for heritability: H(A,B) and H(C,D). These jackknife delete values are estimated by excluding blocks of values (here, number of blocks n = 200). The n-dimensional vectors G(A,B), G(C,D), H(A,B) and H(C,D) can be used to generate genetic correlation delete values R(A,B) and R(C,D). The difference between the global estimates r(A,B) and r(C,D) is d(AB,CD), and the difference between the vectors R(A,B) and R(C,D) is D(AB,CD). The global genetic correlation difference d(AB,CD) and the delete values D(AB,CD) are used to compute jackknife pseudovalues. The ith pseudovalue is:

$$P_i(AB,CD) = n \times d(AB,CD) - (n-1) * P_i(AB,CD)$$

The mean and variance of the jackknife pseudovalues are:

$$m(AB,CD) = \frac{1}{n}\sum_{i=1}^{n} \quad P_i(AB,CD)$$

$$v(AB,CD) = \frac{1}{n-1}\sum_{i=1}^{n} \quad (P_i(AB,CD) - m(AB,CD))^2$$

The jackknife estimate of the difference between the two correlations m(AB,CD) can then be compared to test $H_0 : \theta = \theta_0$ ($\theta_0 = 0$ for no difference between genetic correlations), and a p-value can be derived from the z statistic:

$$z(AB,CD) = \frac{m(AB,CD) - \theta_0}{\sqrt{(1/n) \times v(AB,CD)}}$$

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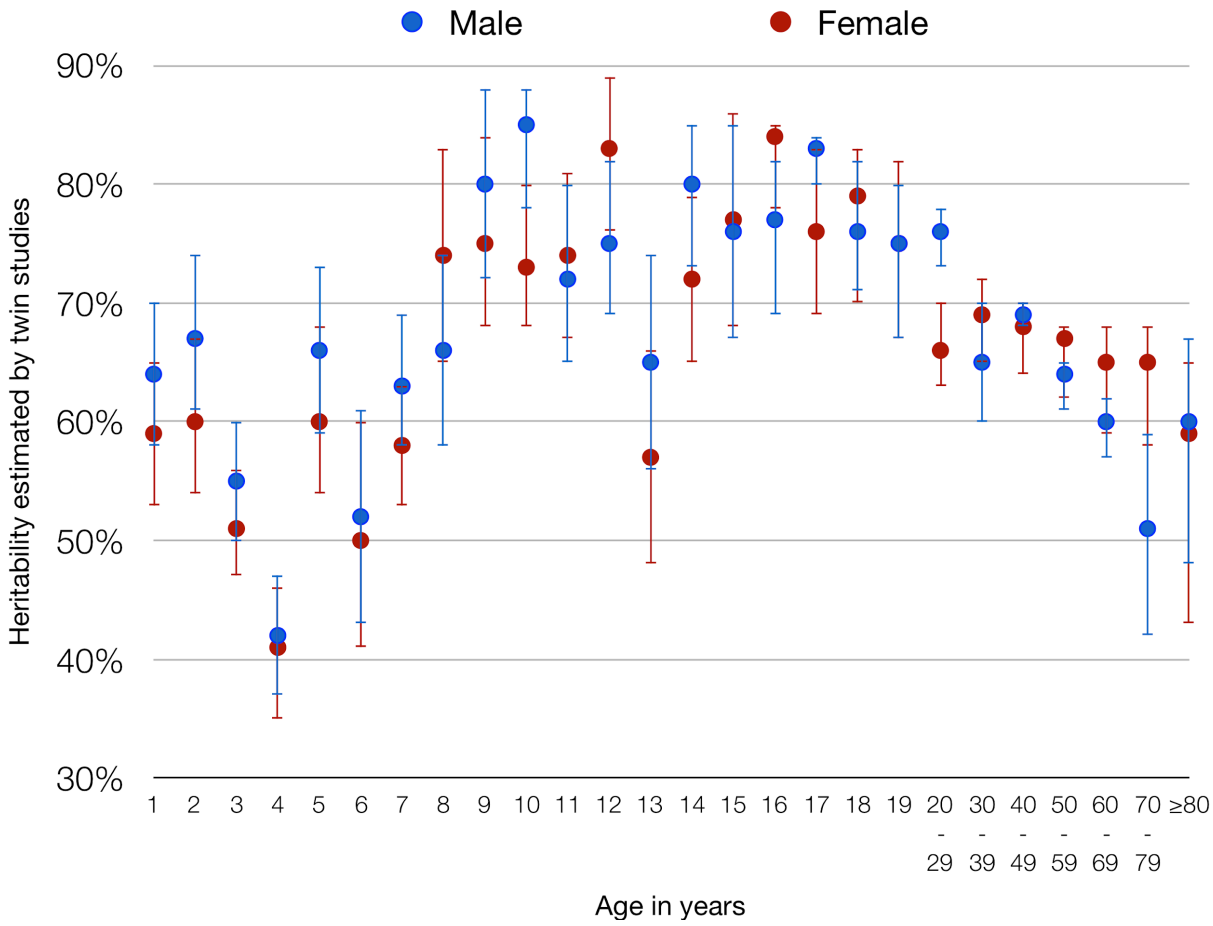
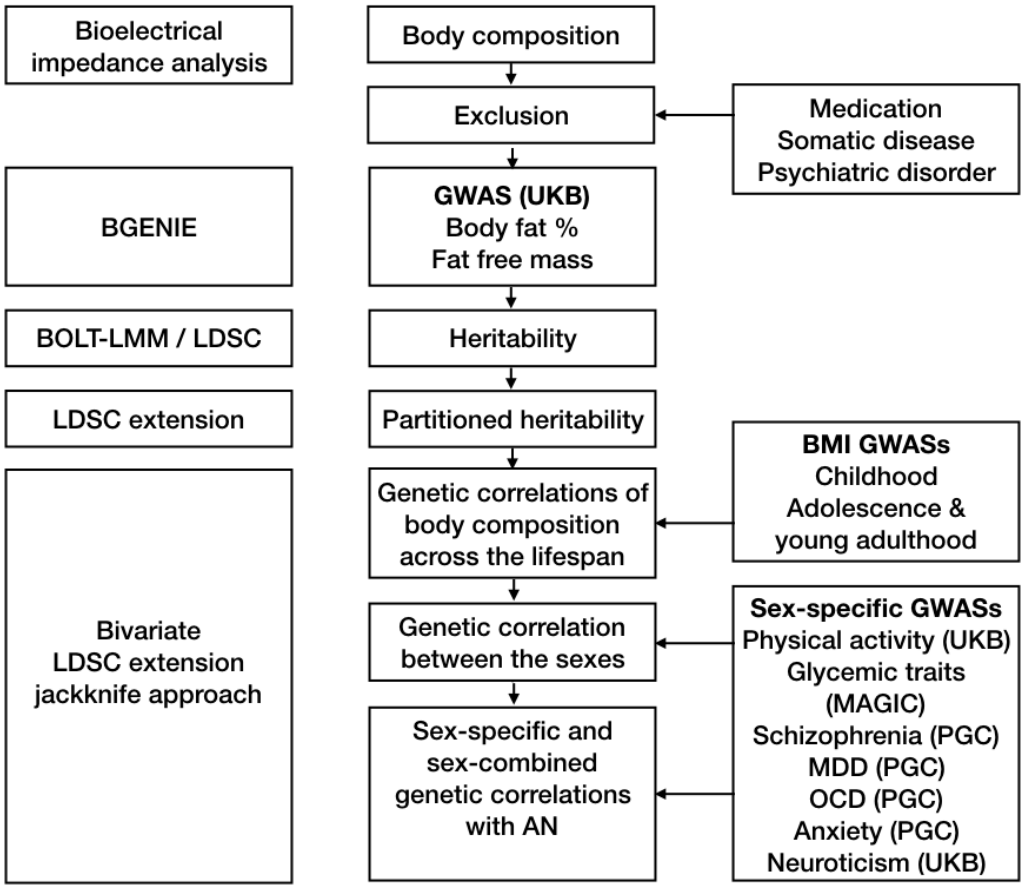
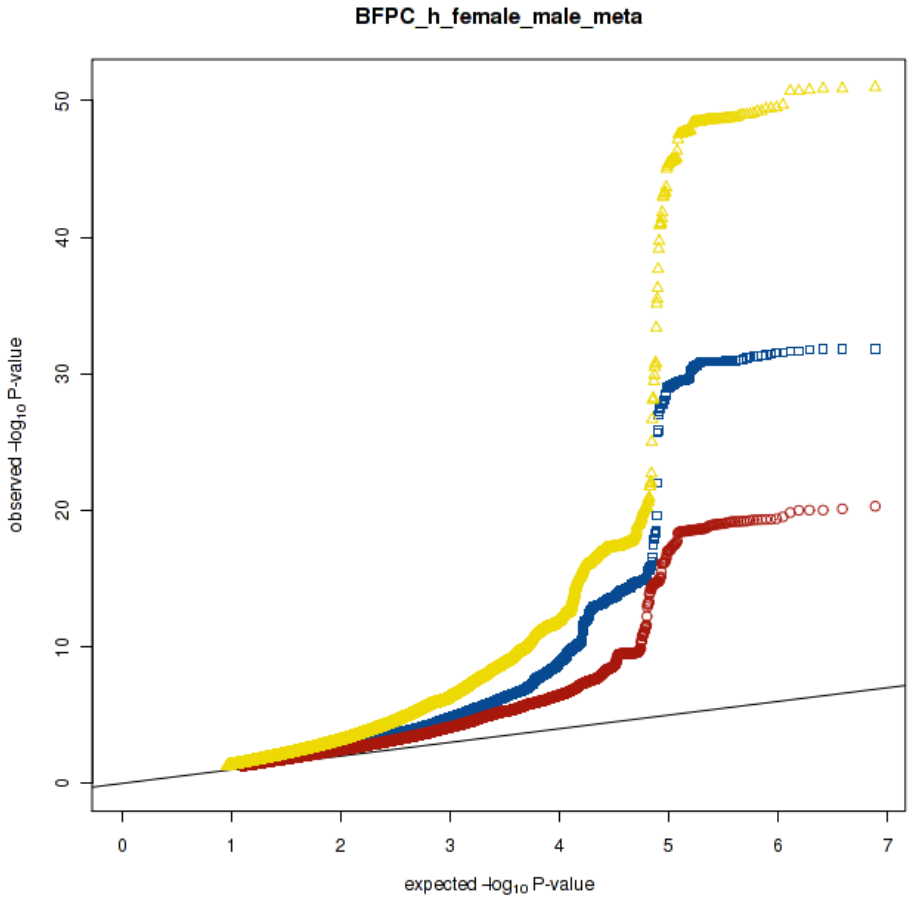
4.2 Supplementary Figures



Supplementary Figure 1. Twin-based heritabilities (*twin-h²*) of body mass index (BMI) across the lifespan as calculated by ACE models from Silventoinen et al. Blue values represent males and red females with error bars depicting 95% confidence intervals (CI 95%). After the age of 19 heritabilities are represented for a whole decade (Silventoinen et al., 2016, 2017).

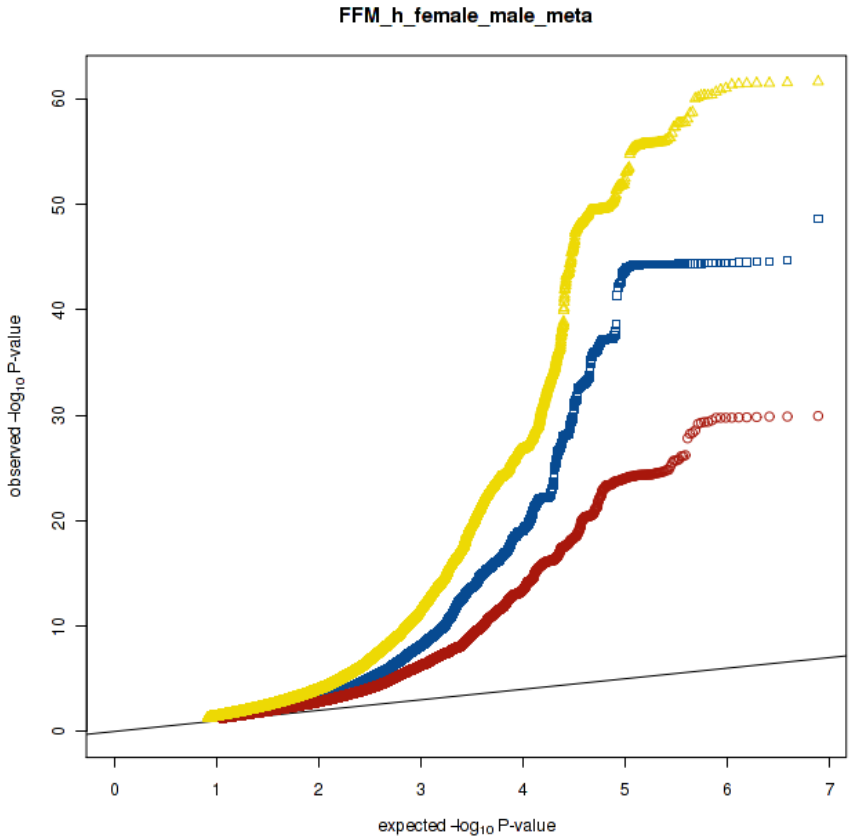


Supplementary Figure 2. Analysis workflow chart. AN = anorexia nervosa, BMI = body mass index, GWAS = genome-wide association study, LDSC = linkage score disequilibrium regression, MAGIC = Meta-Analyses of Glucose and Insulin-related traits Consortium, MDD = major depressive disorder, OCD = obsessive-compulsive disorder, PGC = Psychiatric Genomics Consortium, SSGAC = Social Science Genetic Association Consortium, UKB = UK Biobank



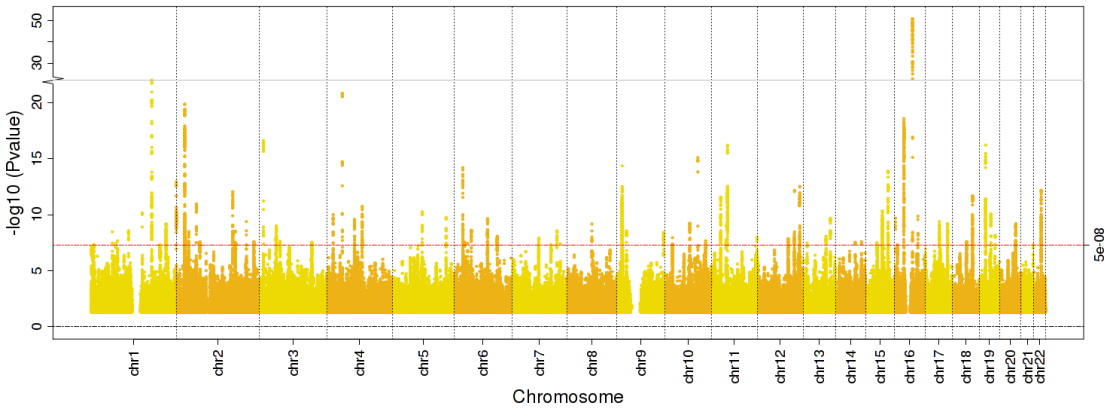
Supplementary Figure 3a. QQ plot for the body fat percentage (BF%) genome-wide-association study (GWAS)

The negative logarithm of the observed (y axis) and the expected (x axis) p value is plotted for each single nucleotide polymorphism (SNP; circle, rectangle or triangle), and the black line indicates the null hypothesis of no true association. Different colours depict the three different GWAS: both sexes (yellow), female (red), male (blue). Deviation from the expected p value distribution is evident only in the tail area, suggesting that population stratification was adequately controlled. BPFC = body fat percentage, h = healthy.

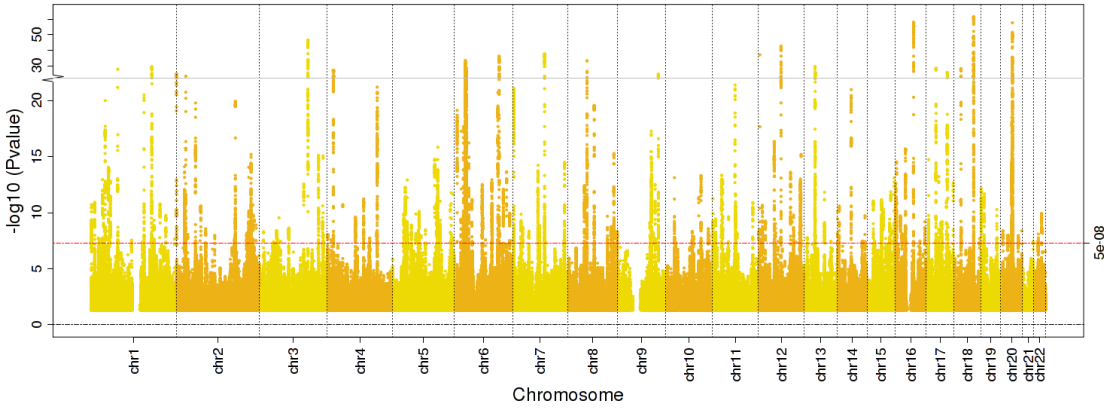


Supplementary Figure 3b. QQ plot for the fat free mass (FFM) genome-wide-association study (GWAS)

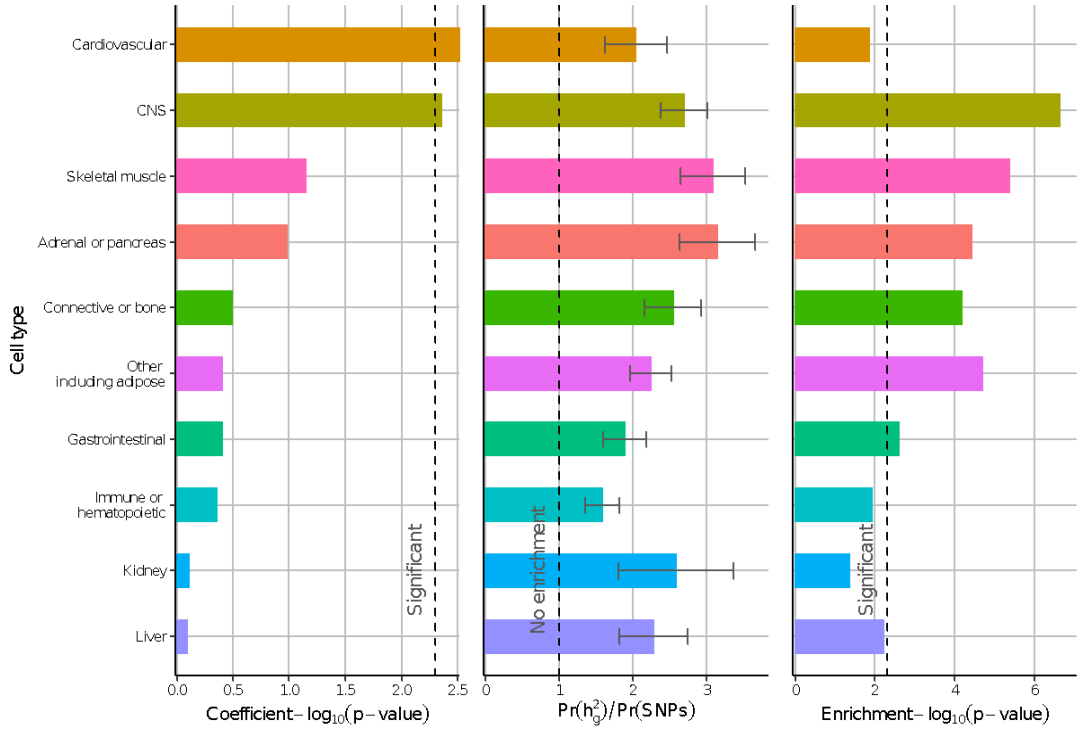
The negative logarithm of the observed (y axis) and the expected (x axis) p value is plotted for each single nucleotide polymorphism (SNP; circle, rectangle or triangle), and the black line indicates the null hypothesis of no true association. Different colours depict the three different GWAS: both sexes (yellow), female (red), male (blue). Deviation from the expected p value distribution is evident only in the tail area, suggesting that population stratification was adequately controlled. FFM = fat free mass, h = healthy.



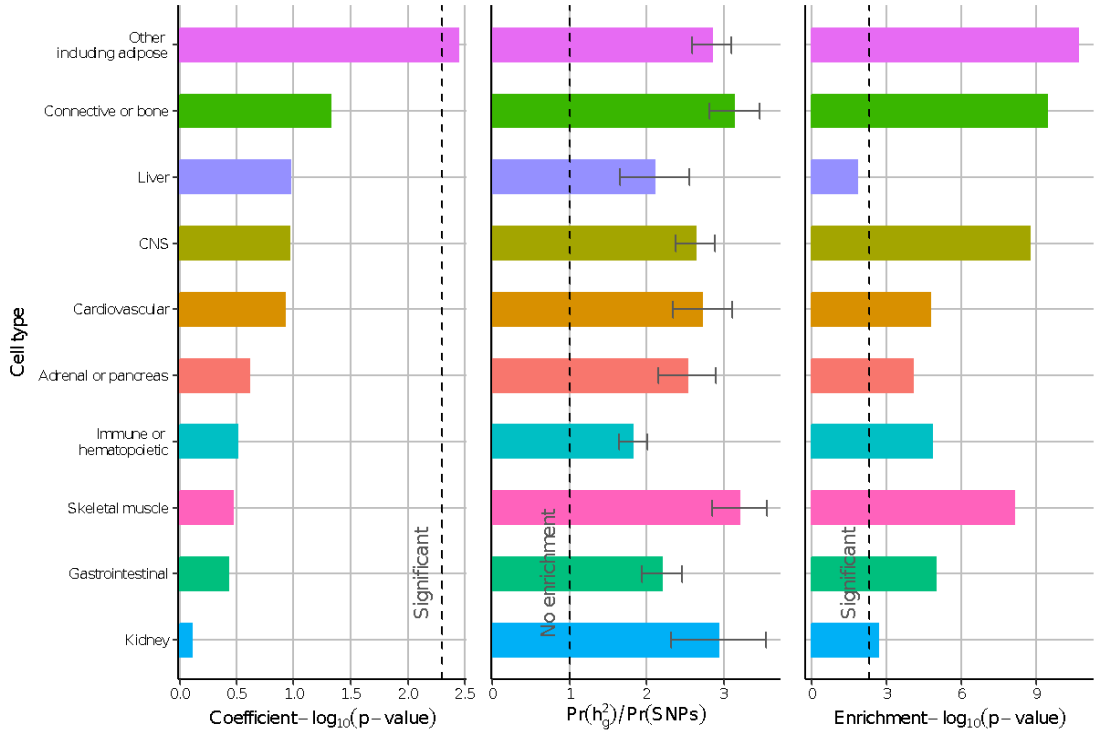
Supplementary Figure 4a. Manhattan plot of the meta-analyzed genome-wide association study (GWAS) of body fat percentage (BF%). The red line represents the genome-wide significance threshold of $5x10^{-8}$. Chr = chromosome.



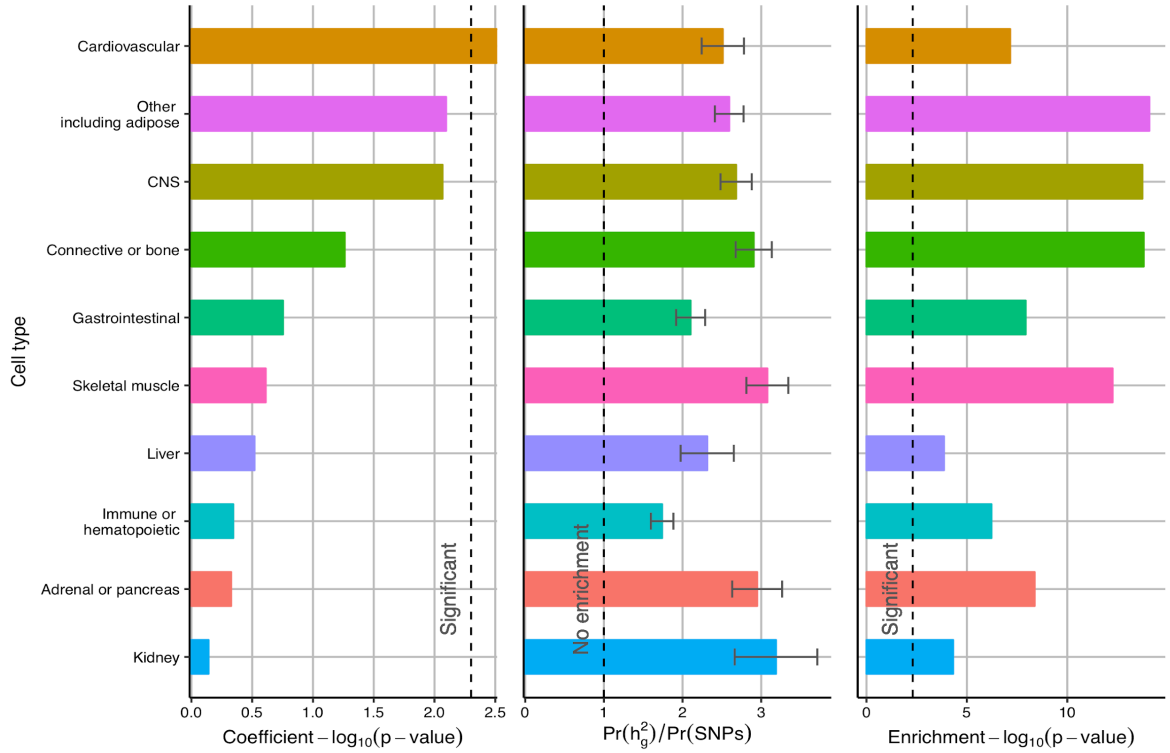
Supplementary Figure 4b. Manhattan plot of the meta-analyzed genome-wide association study (GWAS) of fat free mass (FFM). The red line represents the genome-wide significance threshold of $5x10^{-8}$. Chr = chromosome.



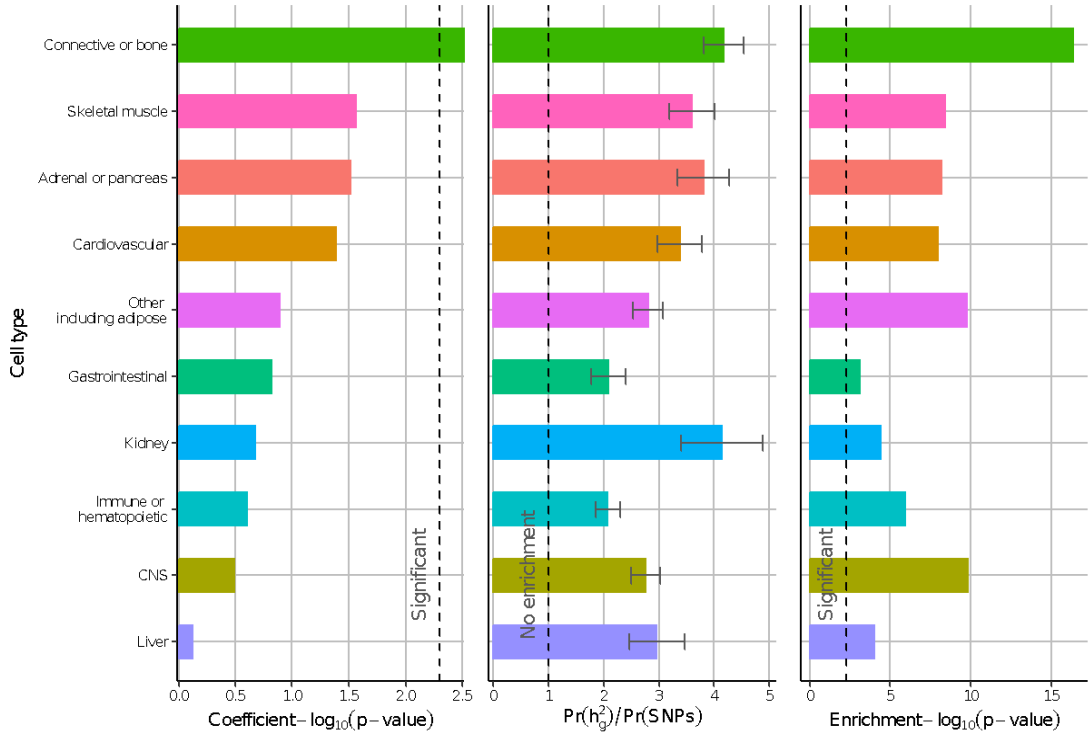
Supplementary Figure 5a. Partitioned heritability by 10 cell type groups for body fat percentage in <u>females</u>. The black dashed lines at $-\log_{10}(P) = 2.3$ is the cutoff for Bonferroni significance. CNS = central nervous system SNP = single nucleotide polymorphism.



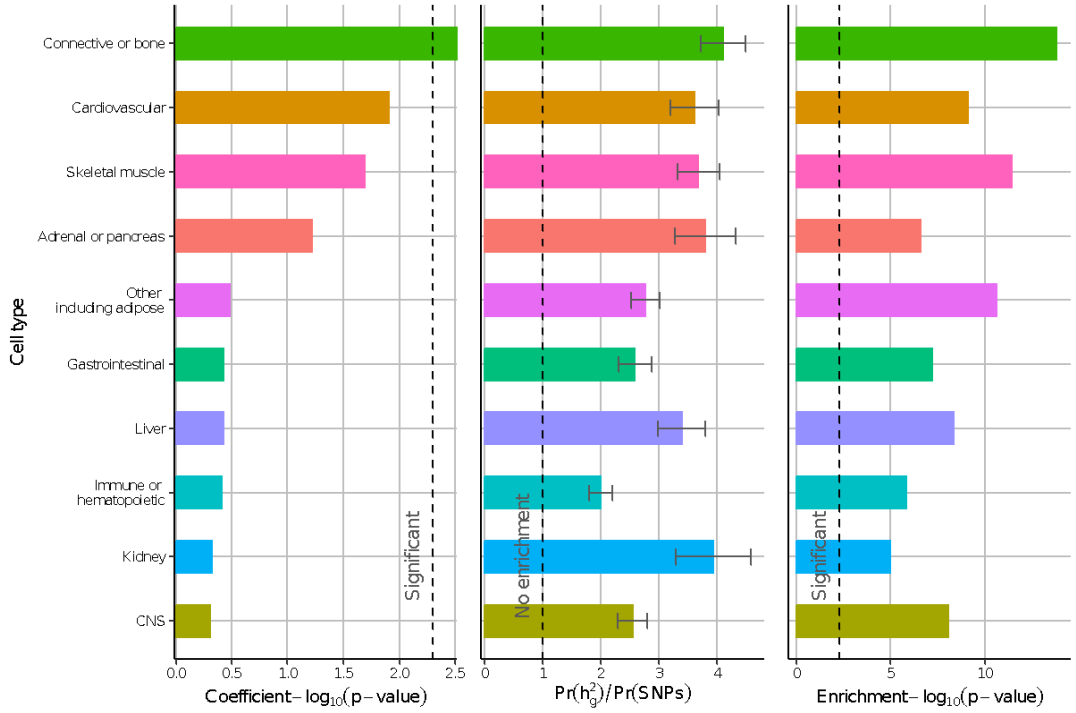
Supplementary Figure 5b. Partitioned heritability by 10 cell type groups for body fat percentage in <u>males</u>. The black dashed lines at $-\log_{10}(P) = 2.3$ is the cutoff for Bonferroni significance. CNS = central nervous system, SNP = single nucleotide polymorphism.



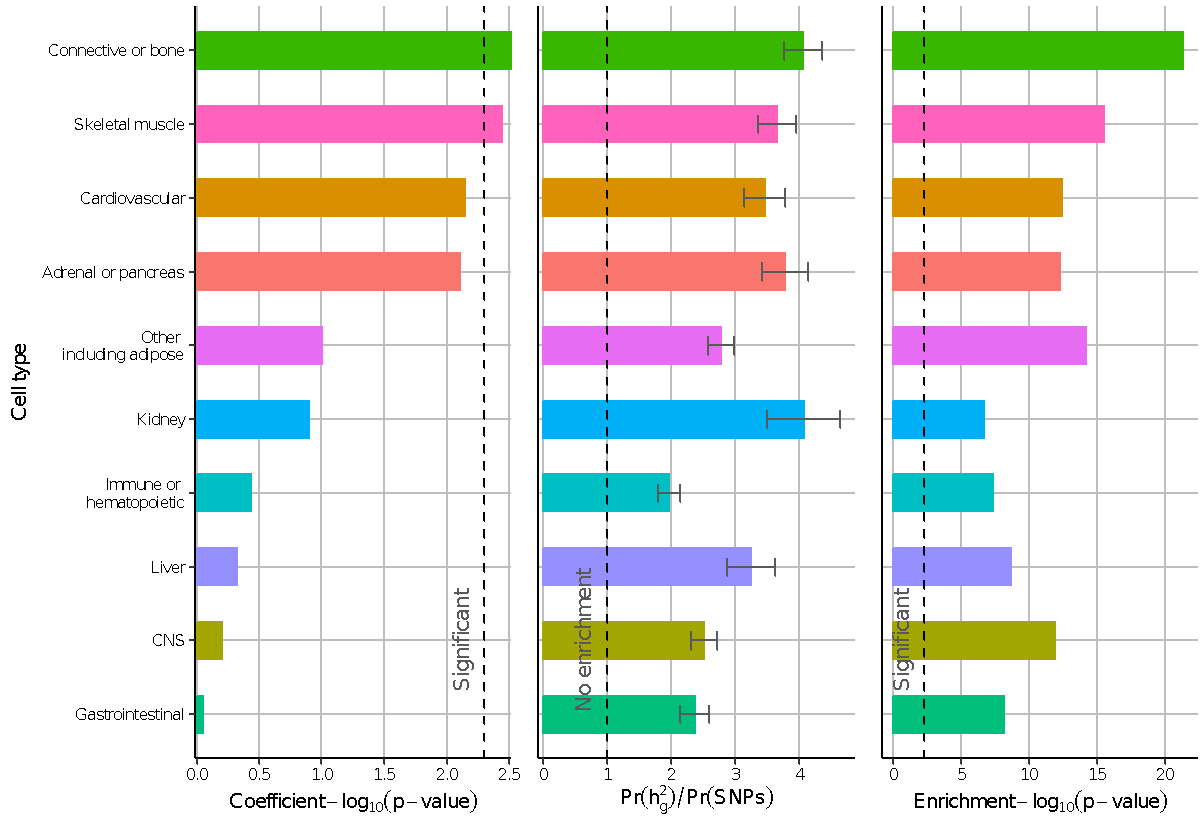
Supplementary Figure 5c. Partitioned heritability by 10 cell type groups for body fat percentage in the meta-analyzed GWAS. The black dashed lines at $-\log_{10}(P) = 2.3$ is the cutoff for Bonferroni significance. CNS = central nervous system, SNP = single nucleotide polymorphism.



Supplementary Figure 6a. Partitioned heritability by 10 cell type groups for fat free mass (FFM) in <u>females</u>. The black dashed lines at $-\log_{10}(P) = 2.3$ is the cutoff for Bonferroni significance. CNS = central nervous system, SNP = single nucleotide polymorphism.



Supplementary Figure 6b. Partitioned heritability by 10 cell type groups for fat free mass (FFM) in <u>males</u>. The black dashed lines at $-\log_{10}(P) = 2.3$ is the cutoff for Bonferroni significance. CNS = central nervous system, SNP = single nucleotide polymorphism.



Supplementary Figure 6c. Partitioned heritability by 10 cell type groups for fat free mass (FFM) in the meta-analyzed GWAS. The black dashed lines at $-\log_{10}(P)$ = 2.3 is the cutoff for Bonferroni significance. CNS = central nervous system, SNP = single nucleotide polymorphism.

Appendix 5 Genetic correlations of psychiatric traits with body composition and glycemic traits are sex- and age-dependent

5.1 Supplementary Material

5.1.1 Tables

Supplementary Table 1 | Phenotypic characteristics of individuals included in the UK Biobank body composition genome-wide association studies (GWASs).

Supplementary Table 2 | Exclusion criteria by International Statistical Classification of Diseases (ICD-10), British National Formulary (BNF), and UK Biobank variable

Supplementary Table 3 | Heritability estimates by linkage disequilibrium score regression, BOLT-LMM, and Haseman-Elston regression

Supplementary Table 4 | Results of the test if genetic correlations between female and male GWAS of body composition, glycemic, psychiatric, and behavioural traits are significantly different from 1.

Supplementary Table 1. Phenotypic characteristics of individuals included in the UK Biobank body composition genome-wide association studies (GWASs).

	Meta-analyzed	Female	Male
Number (%)	155,961	70,700 (45%)	85,261 (55%)
Age, years	54.9 ± 8.1	54.8 ± 8.0	55.0 ± 8.2
Height, cm	170.4 ± 9.3	163.0 ± 6.2	176.4 ± 6.7
Weight, kg	78.1 ± 15.1	69.6 ± 12.6	85.1 ± 13.2
Body mass index, kg/m2	27.0 ± 4.2	26.2 ± 4.6	27.4 ± 3.8
Waist circumference, cm	89.4 ± 12.6	82.3 ± 11.3	95.3 ± 10.3
Hip circumference, cm	102.5 ± 8.1	102.0 ± 9.3	103.0 ± 6.9
Waist-to-hip ratio	0.9 ± 0.1	0.8 ± 0.1	0.9 ± 0.1
Body fat, %	29.3 ± 8.2	35.3 ± 6.7	24.4 ± 5.5
Fat mass, kg	23.0 ± 8.5	25.3 ± 9.1	21.2 ± 7.5
Fat-free mass, kg	55.1 ±11.6	44.4 ± 4.6	63.9 ± 7.4
Socioeconomic status, Townsend Deprivation Index	-1.6 ± 2.9	-1.7 ± 2.8	-1.7 ± 2.9

Data are n (%), or mean (SD).

Alcohol consumption	Freq	% Total	% Total Cum.
Daily or almost daily	34,830	22.3	22.3
Three or four times a week	41,952	26.9	49.2
Once or twice a week	43,055	27.6	76.8
One to three times a month	16,314	10.5	87.3
Special occasions only	12,952	8.3	95.6
Never	6,858	4.4	100.0
Total	155,961	100	100

Tobacco smoking	Freq	% Total	% Total Cum.
No	142,141	91.1	91.1
Only occasionally	9,465	6.1	97.2
Yes, on most or all days	4,355	2.8	100.0
Total	155,961	100	100

Supplementary Table 2. Exclusion criteria by International Statistical Classification of Diseases (ICD-10), British National Formulary (BNF), and UK Biobank variable

International Statistical Classification of Diseases (ICD-10) categories

I Certain infectious and parasitic diseases	
A15-A19	Tuberculosis
B20-B24	Human immunodeficiency virus [HIV] disease
II Neoplasms	
C00-C75	Malignant neoplasms, stated or presumed to be primary, of specified sites, except of lymphoid, haematopoietic and related tissue
C00-C14	Malignant neoplasms of lip, oral cavity and pharynx
C15-C26	Malignant neoplasms of digestive organs
C30-C39	Malignant neoplasms of respiratory and intrathoracic organs
C40-C41	Malignant neoplasms of bone and articular cartilage
C43-C44	Melanoma and other malignant neoplasms of skin
C45-C49	Malignant neoplasms of mesothelial and soft tissue
C50-C50	Malignant neoplasm of breast
C51-C58	Malignant neoplasms of female genital organs
C60-C63	Malignant neoplasms of male genital organs
C64-C68	Malignant neoplasms of urinary tract
C69-C72	Malignant neoplasms of eye, brain and other parts of central nervous system
C73-C75	Malignant neoplasms of thyroid and other endocrine glands
V Mental and behavioural disorders	
F00-F09	Organic, including symptomatic, mental disorders
F10-F19	Mental and behavioural disorders due to psychoactive substance use
F20-F29	Schizophrenia, schizotypal and delusional disorders
F30-F39	Mood [affective] disorders
F40-F48	Neurotic, stress-related and somatoform disorders
F50-F59	Behavioural syndromes associated with physiological disturbances and physical factors
F60-F69	Disorders of adult personality and behaviour
F70-F79	Mental retardation
F80-F89	Disorders of psychological development
F90-F98	Behavioural and emotional disorders with onset usually occurring in childhood and adolescence
F99-F99	Unspecified mental disorder
IV Endocrine, nutritional and metabolic diseases	
E00-E07	Disorders of thyroid gland
E10-E14	Diabetes mellitus
E15-E16	Other disorders of glucose regulation and pancreatic internal secretion
E20-E35	Disorders of other endocrine glands
E70-E90	Metabolic disorders
XI Diseases of the digestive system	
K50-K52	Noninfective enteritis and colitis
K58	Irritable bowel syndrome

K70-K77	Diseases of liver
XIII Diseases of the musculoskeletal system and connective tissue	
M30-M36	Systemic connective tissue disorders
M60-63	Disorders of muscles
Medication - British National Formulary	
A08A	ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS
A10A	INSULINS AND ANALOGUES
A10B	BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS
A10X	OTHER DRUGS USED IN DIABETES
A14A	ANABOLIC STEROIDS
A14B	OTHER ANABOLIC AGENTS
A16A	OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS
C02L	ANTIHYPERTENSIVES AND DIURETICS IN COMBINATION
C03A	LOW-CEILING DIURETICS, THIAZIDES
C03B	LOW-CEILING DIURETICS, EXCL. THIAZIDES
C03C	HIGH-CEILING DIURETICS
C03D	POTASSIUM-SPARING AGENTS
C03E	DIURETICS AND POTASSIUM-SPARING AGENTS IN COMBINATION
C03X	OTHER DIURETICS
C07B	BETA BLOCKING AGENTS AND THIAZIDES
C07C	BETA BLOCKING AGENTS AND OTHER DIURETICS
C07D	BETA BLOCKING AGENTS, THIAZIDES AND OTHER DIURETICS
C09A	ACE INHIBITORS, PLAIN
C09B	ACE INHIBITORS, COMBINATIONS
C09C	ANGIOTENSIN II ANTAGONISTS, PLAIN
C09D	ANGIOTENSIN II ANTAGONISTS, COMBINATIONS
C09X	OTHER AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM
C10A	LIPID MODIFYING AGENTS, PLAIN
C10B	LIPID MODIFYING AGENTS, COMBINATIONS
G03A	HORMONAL CONTRACEPTIVES FOR SYSTEMIC USE
G03B	ANDROGENS
G03C	ESTROGENS
G03D	PROGESTOGENS
G03E	ANDROGENS AND FEMALE SEX HORMONES IN COMBINATION
G03F	PROGESTOGENS AND ESTROGENS IN COMBINATION
G03G	GONADOTROPINS AND OTHER OVULATION STIMULANTS
G03H	ANTIANDROGENS
G03X	OTHER SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
G04CB	Testosterone-5-alpha reductase inhibitors
H01A	ANTERIOR PITUITARY LOBE HORMONES AND ANALOGUES
H01B	POSTERIOR PITUITARY LOBE HORMONES
H01C	HYPOTHALAMIC HORMONES
H02A	CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN
H02B	CORTICOSTEROIDS FOR SYSTEMIC USE, COMBINATIONS
H02C	ANTIADRENAL PREPARATIONS
H03A	THYROID PREPARATIONS
H03B	ANTITHYROID PREPARATIONS
H04A	GLYCOGENOLYTIC HORMONES

H05A	PARATHYROID HORMONES AND ANALOGUES
H05B	ANTI-PARATHYROID AGENTS
J04AC	Hydrazides
J04AD	Thiocarbamide derivatives
J04AK	Other drugs for treatment of tuberculosis
J04AM	Combinations of drugs for treatment of tuberculosis
J04B	DRUGS FOR TREATMENT OF LEPRA
J05AE	Protease inhibitors
J05AF	Nucleoside and nucleotide reverse transcriptase inhibitors
J05AG	Non-nucleoside reverse transcriptase inhibitors
J05AR	Antivirals for treatment of HIV infections, combinations
L01A	ALKYLATING AGENTS
L01B	ANTIMETABOLITES
L01C	PLANT ALKALOIDS AND OTHER NATURAL PRODUCTS
L01D	CYTOTOXIC ANTIBIOTICS AND RELATED SUBSTANCES
L01X	OTHER ANTINEOPLASTIC AGENTS
L02A	HORMONES AND RELATED AGENTS
L02B	HORMONE ANTAGONISTS AND RELATED AGENTS
L03A	IMMUNOSTIMULANTS
L04A	IMMUNOSUPPRESSANTS
M01B	ANTIINFLAMMATORY/ANTIRHEUMATIC AGENTS IN COMBINATION
M01C	SPECIFIC ANTIRHEUMATIC AGENTS
M04A	ANTIGOUT PREPARATIONS
M05B	DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION
M09AA	Quinine and derivatives
N02BG10	Cannabinoids
N04B	DOPAMINERGIC AGENTS
N05A	ANTIPSYCHOTICS
N06A	ANTIDEPRESSANTS
N06BA	Centrally acting sympathomimetics
N06C	PSYCHOLEPTICS AND PSYCHOANALEPTICS IN COMBINATION
UK Biobank	
UK Biobank variable	Pregnancy
UK Biobank variable	Hysterectomie

Supplementary Table 3. Heritability as estimated by BOLT-LMM, v2.3.2, on genotyped single nucleotide polymorphisms (SNPs) on body composition traits in the UK Biobank. Variance explained by BOLT-LMM's linear predictor—using the default mixture-of-Gaussians prior on SNP effect sizes, which accounts for larger-effect SNPs—and variance theoretically explained by an optimal linear predictor, i.e., SNP-heritability (h2g). Additionally, heritability estimates and genetic correlations from linkage disequilibrium score regression (LDSC; Bulik-Sullivan et al., 2015) and Haseman-Elston regression analysis (HEreg; Yang et al., 2017).

Phenotype	Sex	Optimal linear predictor (h2e)	SE	BOLT-LMM Optimal linear predictor (h2g)	SE	n SNPs	n individuals	LDSC h2	SE	Difference: BOLT-LDSC	HEreg	SE
Body fat %	both	71.1%	0.4%	28.9%	0.4%	560011	155951	20.2%	0.7%	8.7%	21.9%	0.6%
	female	68.9%	0.8%	31.1%	0.8%	560011	70693	20.3%	1.0%	10.8%	22.8%	1.0%
	male	66.2%	0.7%	33.8%	0.7%	560011	85258	22.7%	0.9%	11.1%	25.2%	0.9%
	rg							0.89	0.03		0.913	0.027
Body mass index	both	70.4%	0.4%	29.6%	0.4%	560011	155951	21.2%	0.8%	8.4%	23.8%	0.7%
	female	69.7%	0.8%	30.3%	0.8%	560011	70693	19.9%	1.1%	10.4%	22.7%	1.2%
	male	64.4%	0.7%	35.6%	0.7%	560011	85258	23.5%	1.1%	12.0%	27.8%	1.2%
								0.954	0.02		0.946	0.027
Fat mass	both	70.9%	0.4%	29.1%	0.4%	560011	155951	20.4%	0.7%	8.7%	23.8%	0.8%
	female	68.8%	0.8%	31.2%	0.8%	560011	70693	20.5%	1.0%	10.7%	24.5%	1.4%
	male	66.7%	0.7%	33.3%	0.7%	560011	85258	21.8%	1.0%	11.5%	25.8%	1.1%
	rg							0.95	0.03		0.947	0.027
Fat-free mass	both	57.3%	0.4%	42.7%	0.4%	560011	155951	27.3%	1.1%	15.4%	43.0%	1.2%
	female	56.9%	0.8%	43.1%	0.8%	560011	70693	29.4%	1.5%	13.7%	41.3%	2.0%
	male	49.5%	0.7%	50.5%	0.7%	560011	85258	32.3%	1.7%	18.2%	48.5%	1.9%
	rg							0.95	0.02		0.962	0.016

Abbreviations: h2e = environment/noise, h2/h2g = common genetic variant heritability, LDSC = linkage disequilibrium score regression, n = number, SE = standard error, SNP = single nucleotide polymorphism

Supplementary Table 4. Results of the test if genetic correlations between female and male GWAS of body composition, glycemic, psychiatric, and behavioural traits are significantly different from 1. The correlations were calculated using linkage disequilibrium score regression (Bulik-Sullivan et. al, 2015). Standard errors were calculated by a block jackknife approach described in Hübel et al. 2018. Bonferroni-corrected p value threshold: alpha = 0.05/28 = 0.0018. Abbreviations: BF% = body fat percentage, blocks = number of blocks used for the estimation of the jackknife standard error, BMI = body mass index, FFM = fat-free mass, FM = fat mass, HOMA-IR = Homeostatic Model Assessment for Insulin Resistance, nominally = significant at alpha = 0.02, rg = genetic correlation, se = standard error, sign = statistically significant after multiple testing correction, UKB = UK Biobank, var = variance, vs = versus

Phenotypes Female vs male	**code**	**rg**	**se**	**blocks**	**var**	**se**	**estimate**	**z score**	**p (rg!=1)**	**sign 0.0018**	**nominally**
Attention deficit hyperactivity disorder (ADHD)	ADHD05	NA		NA	NA	NA	NA	NA	NA		
Alcohol dependence	ALCD03	0.76	1.57	200	2.458	1.57	-2.18	-2.03	0.04		nominally
Anxiety	ANXI03	0.98	0.11	200	0.012	0.11	0.98	-0.22	0.82		
Autism spectrum disorder (ASD)	AUTI06	0.29	0.09	200	0.009	0.09	0.28	-7.80	6.38E-15	significant	nominally
Bipolar disorder	BIPO02	0.89	0.05	200	0.002	0.05	0.90	-2.21	0.03		nominally
Major depressive disorder (MDD)	DEPR03	0.96	0.21	200	0.104	0.32	0.85	-0.46	0.64		
Education years	EDUC01	0.92	0.02	200	0.000	0.02	0.91	-3.94	7.99E-05	significant	nominally
Insomnia	INSO01	0.78	0.12	200	0.014	0.12	0.77	-1.93	0.05		
Migraine	MIGR01	0.82	0.17	200	0.031	0.17	0.78	-1.28	0.20		
Neuroticism	NEUR03	0.99	0.06	200	0.003	0.06	0.98	-0.41	0.68		
Obsessive compulsive disorder (OCD)	OCDI01	0.98	0.51	200	0.260	0.51	0.75	-0.50	0.62		
Post-traumatic stress disorder (PTSD)	PTSD03	0.00	0.58	200	0.331	0.58	0.07	-1.62	0.11		
Schizophrenia	SCHI02	0.94	0.03	200	0.001	0.03	0.94	-2.26	0.02		nominally

Body composition Female vs male	-		-	-	-	-	-	-	-	-	
Body mass index (UKB)	BODY07	0.95	0.03	200	0.001	0.03	0.95	-1.72	0.09		
Body mass index adolescence/young adulthood	BODY12	NA		NA	NA	NA	NA	NA	NA		
Fat-free mass healthy	LEAN05	0.95	0.02	200	0.001	0.02	0.95	-2.09	0.04		nominally
Body fat % healthy	BFPC03	0.89	0.03	200	0.001	0.03	0.90	-3.50	4.67E-04	significant	nominally
Fat mass healthy	FATM03	0.95	0.03	200	0.001	0.03	0.95	-1.87	0.06		
Age groups BMI											
Childhood vs. adolescence	BODY09/12	1.01	0.07	200	0.005	0.07	1.01	0.10	0.92		
Childhood vs. UKB healthy	BODY09/07	0.66	0.04	200	0.001	0.04	0.66	-9.09	1.03E-19	significant	nominally
Adolescence vs UKB healthy	BODY12/07	0.80	0.05	200	0.002	0.05	0.80	-4.27	1.94E-05	significant	nominally
Fat-free mass											
Childhood UKB healthy	LEAN01/ LEAB05B	0.30	0.04	200	0.002	0.04	0.30	-16.53	2.33E-61	significant	nominally
Body compartments											
BF% vs. BMI healthy	BFPC03/ BODY07	0.82	0.01	200	0.000	0.01	0.82	-19.61	1.22E-85	significant	nominally
BF% vs FFM healthy	BFPC03/ LEAN05	0.26	0.02	200	0.001	0.02	0.29	-29.17	4.28E-187	significant	nominally
BMI vs. FFM healthy	BODY07/ LEAN05	0.52	0.02	200	0.000	0.02	0.51	-23.48	7.01E-122	significant	nominally
Glycemic traits Female vs. male											
HOMA-IR: Insulin resistance	GLYC16	0.76	0.16	200	0.024	0.16	0.74	-1.66	0.10		
Fasting insulin	GLYC18	0.72	0.12	200	0.015	0.12	0.70	-2.45	0.01		nominally
Fasting glucose	GLYC19	0.82	0.07	200	0.004	0.07	0.83	-2.57	0.01		nominally
Energy expenditure Female vs. male											
Physical activity	PHYS01	1.00	0.09	200	0.008	0.09	0.99	-0.0639	0.95		

5.1.2 Figures

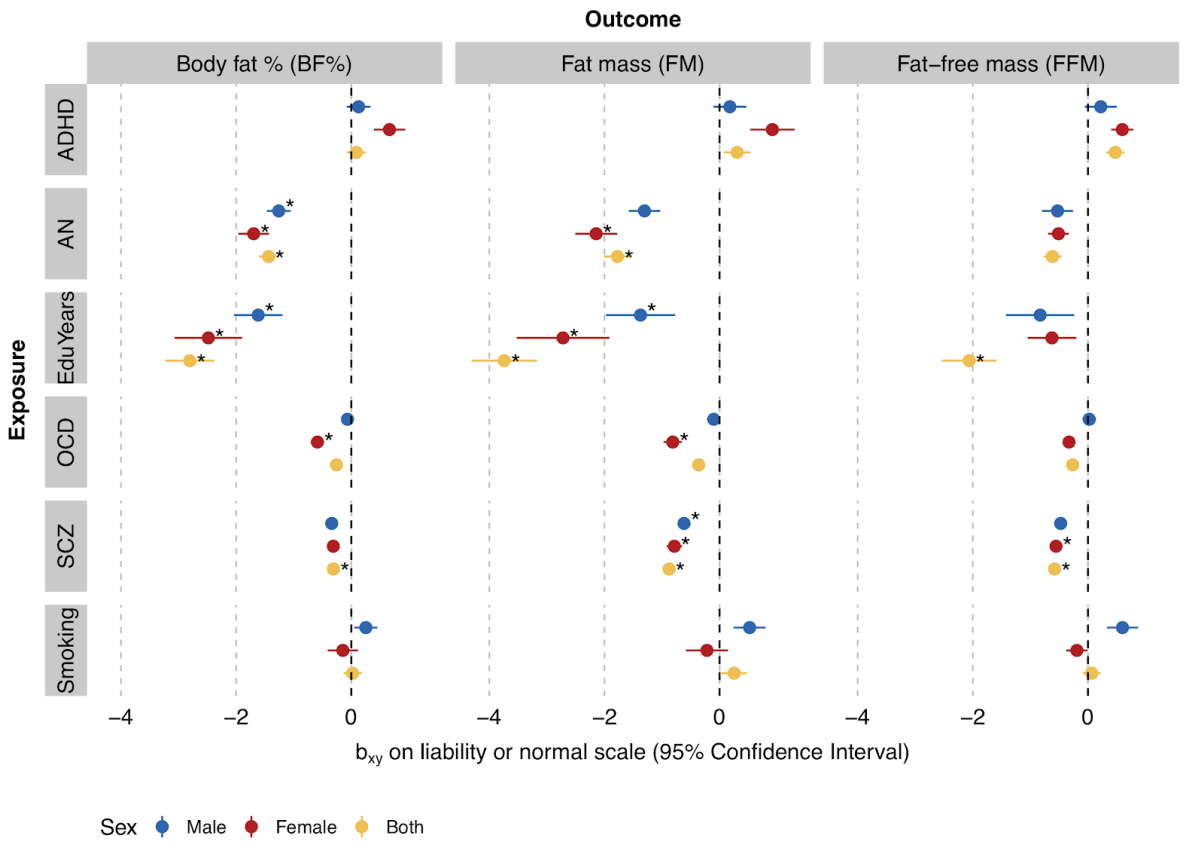
Supplementary Fig. 1 | Putative causal associations of exposures psychiatric disorders and behavioural traits with outcomes body composition traits.

Supplementary Fig. 2a | Sex-specific genetic correlations of body composition traits and physical activity with psychiatric disorders and behavioural traits for females only.

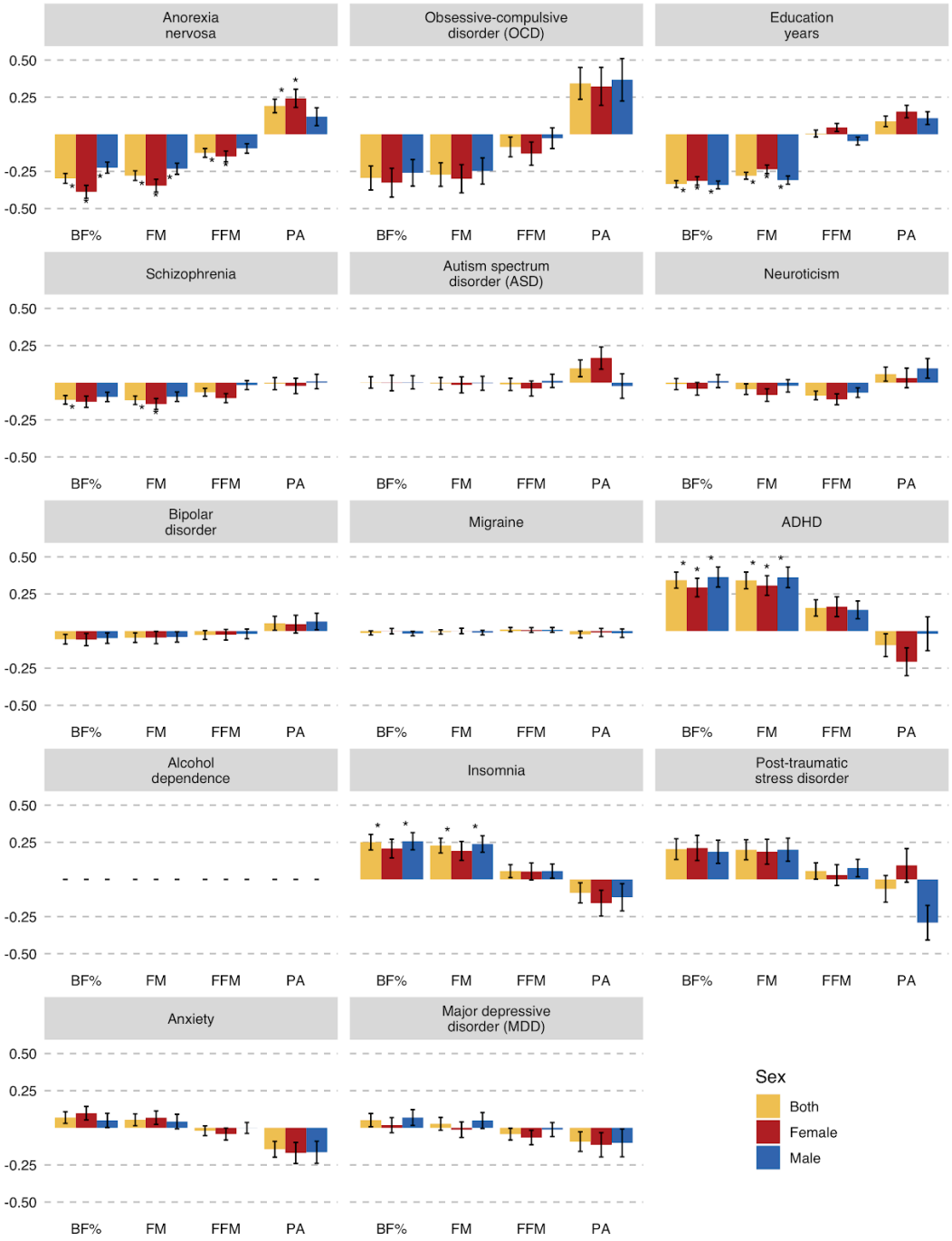
Supplementary Fig. 2b | Sex-specific genetic correlations of body composition traits and physical activity with psychiatric disorders and behavioural traits for males only.

Supplementary Fig. 3a | Sex-specific genetic correlations of glycemic traits of psychiatric disorders and behavioural traits for females only.

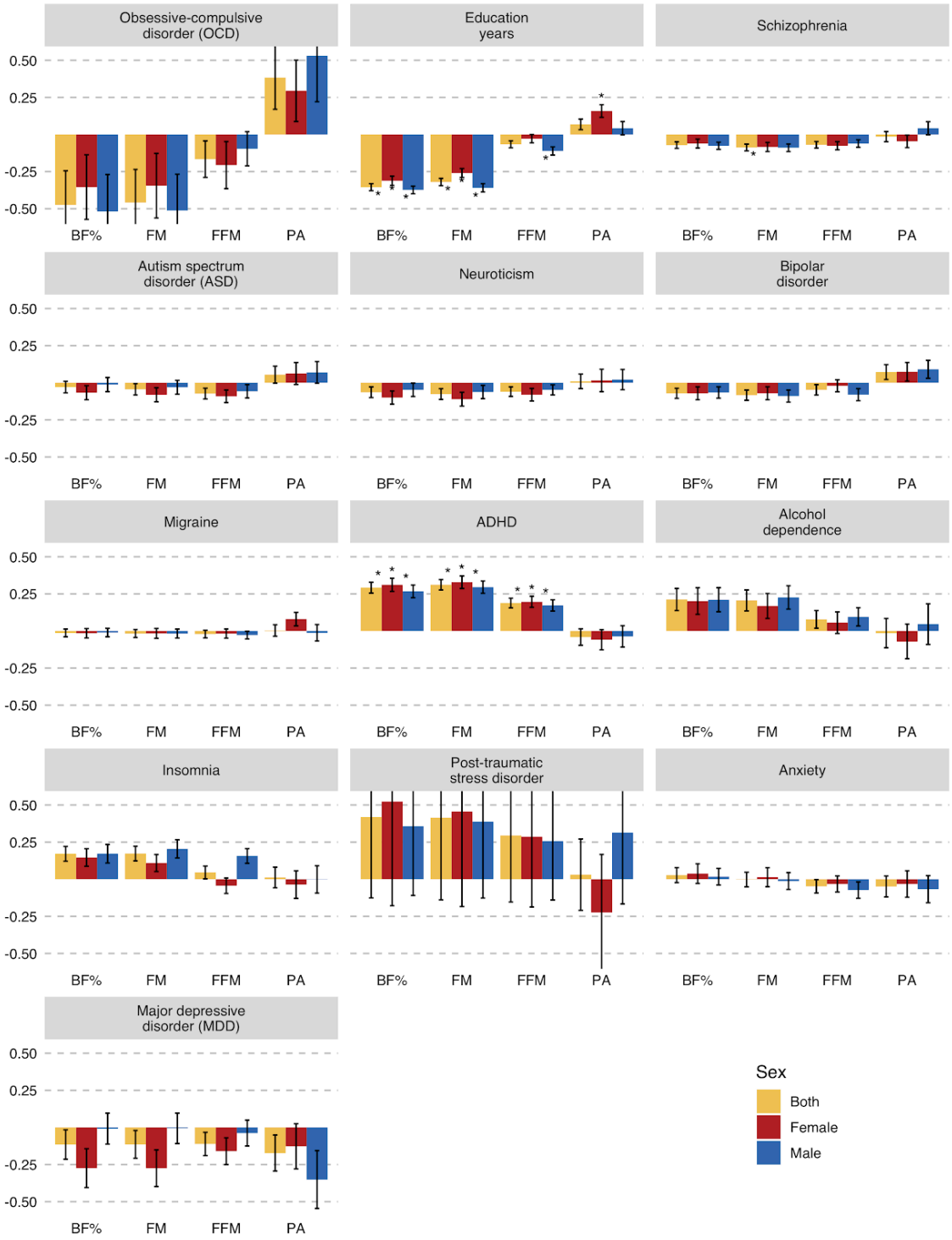
Supplementary Fig. 3b | Sex-specific genetic correlations of glycemic traits of psychiatric disorders and behavioural traits for males only.



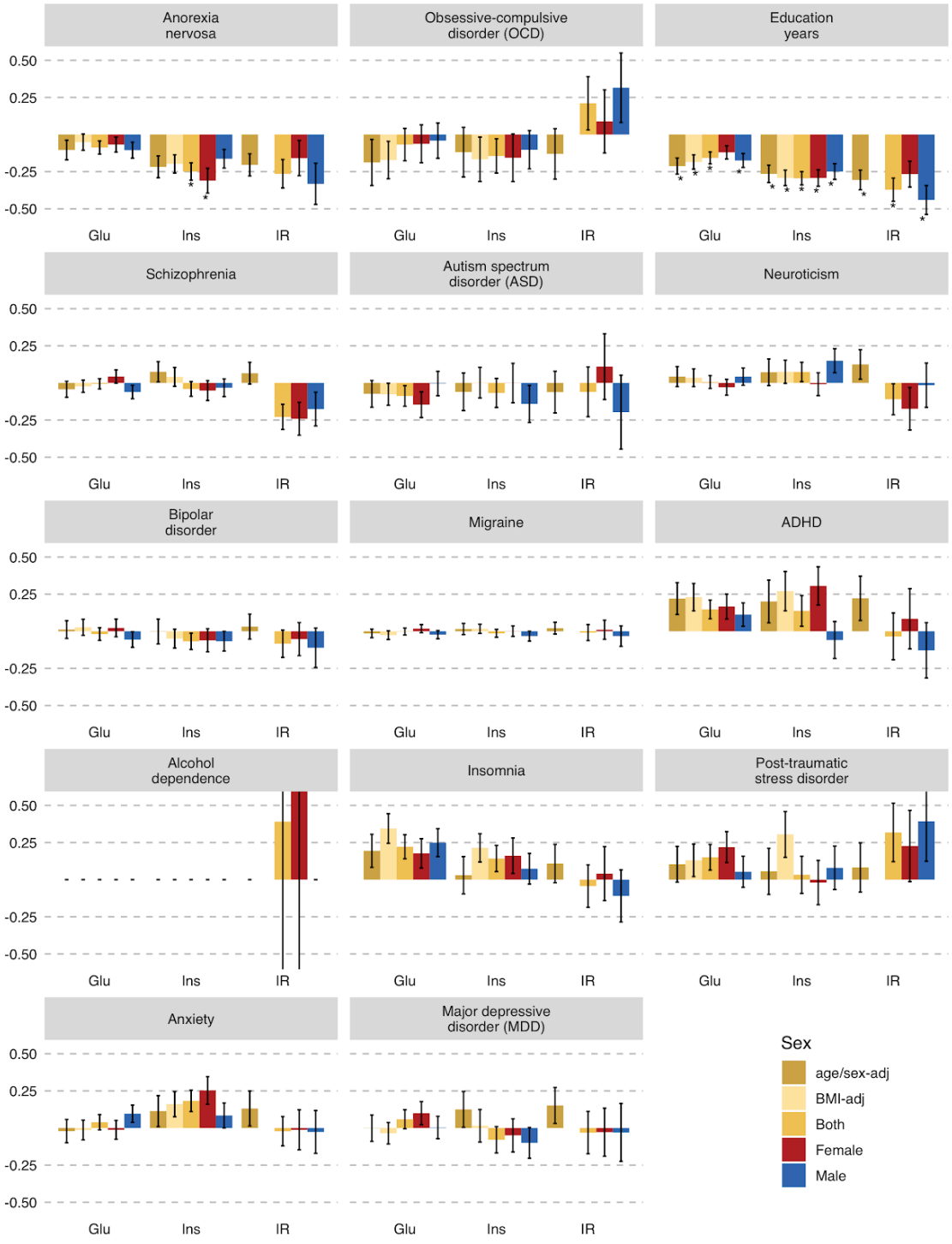
Supplementary Fig. 1 | Putative causal associations of exposures (rows) psychiatric disorders (n = up to 77,096) and behavioural traits (n = up to 217,568) with outcomes (columns) body composition traits (n = up to 155,961). Results are shown from generalised summary data-based Mendelian randomization (GSMR) analyses. Dots represent the effect sizes (as measured by betas, b_{xy}) of risk factors on disorders or traits. Colors represent the sex of the body composition trait genome-wide association study (GWAS): red for female effects, blue for male effects, and yellow for sex-combined effects. Error bars represent 95% confidence intervals (95% CIs). BF% = body fat percentage, FFM = fat-free mass, FM = fat mass, ADHD = attention-deficit/hyperactivity disorder, AN = anorexia nervosa, EduYears = education years, OCD = obsessive-compulsive disorder, SCZ = schizophrenia



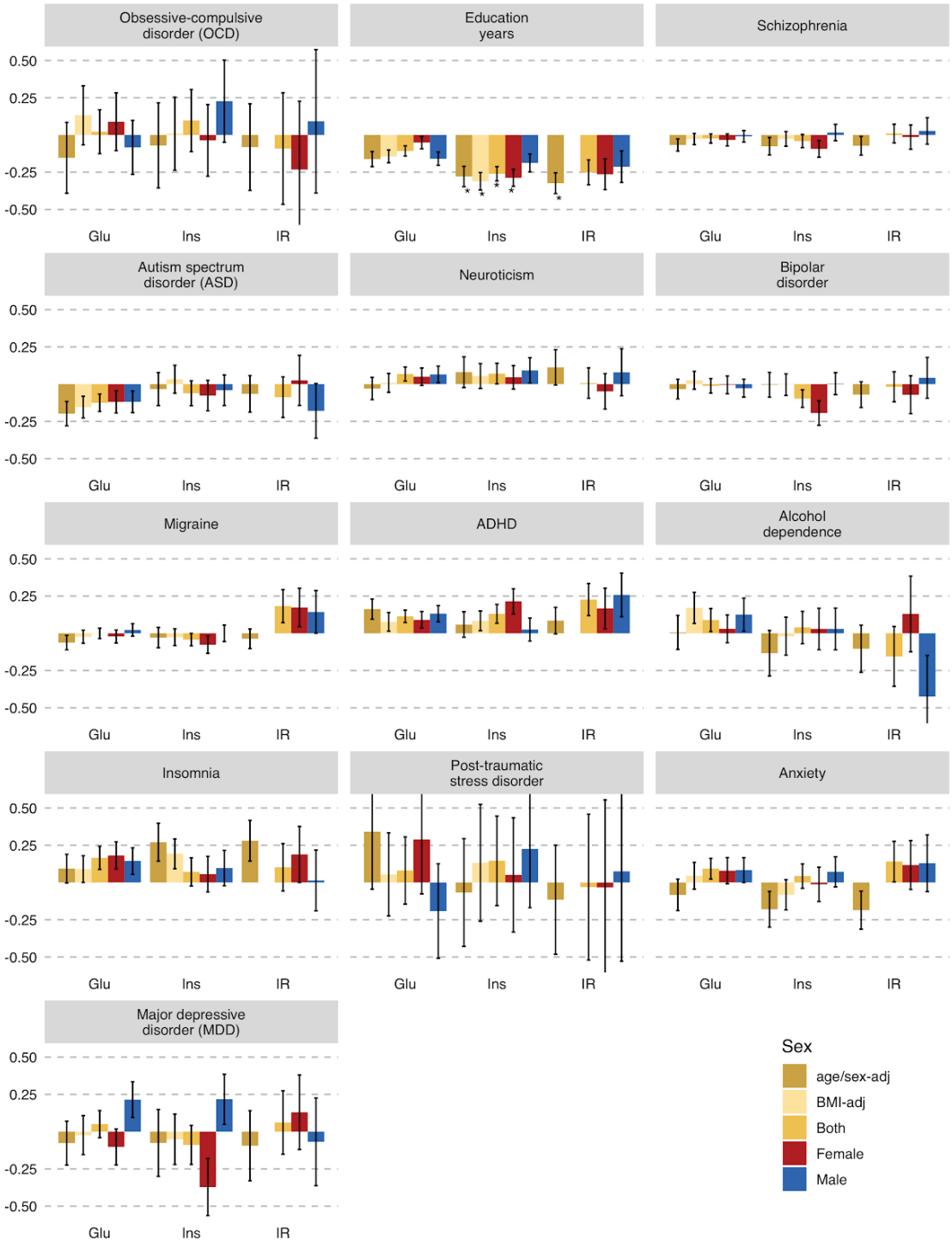
Supplementary Fig. 2a | Sex-specific genetic correlations of body composition traits (n = up to 155,961) and physical activity (n = up to 66,224) with psychiatric disorders (n = up to 35,585) and behavioural traits (n = up to 122,428) for females only. The autosomal genetic correlations were calculated by bivariate linkage disequilibrium score regression (LDSC). Colored bars represent genetic correlations, error bars depict standard errors (SE) and asterisks indicate statistically significant genetic correlations with p values less than α =0.0003. This threshold was calculated via the identification of the number of independent tests using matrix decomposition of the genetic correlation matrix and subsequent Bonferroni correction of α = 0.05 for 190 independent tests. ADHD = attention-deficit/hyperactivity disorder, BF% = body fat percentage, FFM = fat-free mass, FM = fat mass, PA = physical activity



Supplementary Fig. 2b | Sex-specific genetic correlations of body composition traits (n = up to 155,961) and physical activity (n = up to 66,224) with psychiatric disorders (n = up to 45,699) and behavioural traits (n = up to 95,140) for <u>males only</u>. The autosomal genetic correlations were calculated by bivariate linkage disequilibrium score regression (LDSC). Colored bars represent genetic correlations, error bars depict standard errors (SE) and asterisks indicate statistically significant genetic correlations with p values less than α =0.0003. This threshold was calculated via the identification of the number of independent tests using matrix decomposition of the genetic correlation matrix and subsequent Bonferroni correction of α = 0.05 for 190 independent tests. ADHD = attention-deficit/hyperactivity disorder, BF% = body fat percentage, FFM = fat-free mass, FM = fat mass, PA = physical activity



Supplementary Fig. 3a | Sex-specific genetic correlations of glycemic traits (n = up to 140,583) with psychiatric disorders (n = up to 45,699) and behavioural traits (n = up to 95,140) for females only. The autosomal genetic correlations were calculated by bivariate linkage disequilibrium score regression (LDSC). Colored bars represent genetic correlations, error bars depict standard errors (SE) and asterisks indicate statistically significant genetic correlations with p values less than α =0.0002. This threshold was calculated via the identification of the number of independent tests using matrix decomposition of the genetic correlation matrix and subsequent Bonferroni correction of α = 0.05 for 231 independent tests. ADHD = attention-deficit/hyperactivity disorder, Glu = fasting glucose, Ins = fasting insulin, IR = insulin resistance, adj = adjusted



Supplementary Fig. 3b | Sex-specific genetic correlations of glycemic traits (n = up to 140,583) of psychiatric disorders (n = up to 45,699) and behavioural traits (n = up to 95,140) for <u>males only</u>. The autosomal genetic correlations were calculated by bivariate linkage disequilibrium score regression (LDSC). Colored bars represent genetic correlations, error bars depict standard errors (SE) and asterisks indicate statistically significant genetic correlations with p values less than α =0.0002. This threshold was calculated via the identification of the number of independent tests using matrix decomposition of the genetic correlation matrix and subsequent Bonferroni correction of α = 0.05 for 231 independent tests. ADHD = attention-deficit/hyperactivity disorder, Glu = fasting glucose, Ins = fasting insulin, IR = insulin resistance, adj = adjusted

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Meta-Analyses of Glucose and Insulin-related traits consortium (MAGIC)

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